

Post Approval Submissions

Modification Information

To modify an approved study, edit the individual answers that make up the application. The questions below are intended solely for the IRB to have a summary statement of your requested action. The modifications cannot be processed until the actual changes have been made throughout the application.

1. Provide a brief non-technical summary of any changes you will be making to the study (i.e., study application, project personnel, and/or study documents.) The text you enter here will be reproduced in the IRB approval document, and should contain the details that you and/or your sponsor find relevant (e.g., master protocol/amendment version number and date). Typical summaries are 50-100 words. PLEASE NOTE: THIS SECTION MAY BE EDITED BY THE IRB FOR CLARITY OR LENGTH.

This modification is for the addition of two study measurements that will only be implemented with new subjects once final IRB approval is complete. These study measurements will not increase study participation risk. Sections A.4 and A.6 have been modified to reflect these changes and the consent form has been updated as well. The study measurements include the addition of an electronic survey administered by study staff on a study specific Iphone application called TrackMyAir and the other is the use of an overnight compression shirt that measures ventilation called a Hexoskin. Supporting documents will be attached.

We would also like to increase the number of screened subjects to account for subjects that enrolled but did not completed all 5 study sessions, so that we may achieve our enrollment goal of 60 total completed subject data sets.

2. Is this study in Data Analysis only (i.e. enrollment, intervention and follow-up are complete)?

No

Total number of subjects enrolled to date:

59

Is this study currently open to the enrollment of new subjects?

Yes

Total number of subjects actively participating (i.e., Total number of subjects involved in the interventional part of this study. If the study is limited to data collection (e.g., surveys, questionnaires, collection of data from existing records), enter '0':

2

3. Do you have plans to re-consent subjects as a result of this modification?

No

4. Is this modification being submitted in response to New Safety Information?

No

5. Have the risks as described in A.6., consent form, or any other study document changed?

This may include new risks not previously listed, changes in frequency of known risks, or removal of previously listed risks.

No

Continuing with Modifications

Click the "save and continue" button to access your existing application.
You may make any changes to the application that you are requesting at this time.

General Information

1. General Information

1. Project Title

Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

2. **Brief Summary.** Provide a **brief non-technical description** of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content. PLEASE NOTE: THIS SECTION MAY BE EDITED BY THE IRB FOR CLARITY OR LENGTH.

Purpose: To examine the relationship between blood levels of dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and cardiopulmonary responses to environmental air pollution in healthy adults. EPA and DHA are two important omega-3 fatty acids that are mainly found in seafoods and fish oils and associated with beneficial effects to human physiology.

Participants: Healthy 25-55 year-old male and female subjects will be pre-screened for their dietary intake of EPA and DHA. Qualified volunteers will be divided into two groups, group 1: individuals voluntarily taking at least 3 g/wk of EPA and DHA from dietary sources including fish oil supplements and ocean fish/shellfish consumption for a period of at least 6 months prior to enrollment in the study; group 2: individuals who have consumed no more than 1 serving size (4-6 oz)/month of ocean fish/shellfish, or no more than 1 pill/month of fish oil supplement during the 6 month period preceding enrollment. Then volunteers will complete a blood omega-3 index screening. Subjects from group 1 with omega-3 index of approximately 5.5% or higher, and subjects from group 2 with omega-3 index of approximately 4% or lower will be considered for the study.

Procedures (Methods): In this observational panel study, subjects will come to the U.S. EPA Human Studies Facility for up to 5 sessions, each consisting of 2 consecutive visit days. The following endpoints will be collected: blood pressure, heart rate variability (HRV) measurements, venous blood, brachial artery diameter, retinal venule and arteriole diameter, and spirometry. Study participants will be exposed to environmental level of air pollution. Air pollution exposure will be assessed using area-specific air quality data derived from local air monitoring stations interfaced with activity monitoring, GPS tracked location, Hexoskin and TrackMyAir data for each subject.

2. Project Personnel

1. Will this project be led by a STUDENT (undergraduate, graduate) or TRAINEE (resident, fellow, postdoc), working in fulfillment of requirements for a University course, program or fellowship?

No







2. List all project personnel beginning with principal investigator, followed by faculty advisor, co-investigators, study coordinators, and anyone else who has contact with subjects or identifiable data from subjects.

- List ONLY those personnel for whom this IRB will be responsible; do NOT include collaborators who will remain under the oversight of another IRB **for this study**.
- If this is Community Based Participatory Research (CBPR) or you are otherwise working with community partners (who are not functioning as researchers), you may not be required to list them here as project personnel; consult with your IRB.
- If your extended research team includes multiple individuals with limited roles, you may not be required to list them here as project personnel; consult with your IRB.

The table below will access campus directory information; if you do not find your name, your directory listing may need to be updated.

If a change to the Principal Investigator is requested during the course of the study, a [PI Change Form](#) must be submitted.

University of North Carolina at Chapel Hill (UNC-CH)							
Full Name	Role	IRB Training	GCP COI Number	Initial COI Disclosure	Potential Conflict	COI Review Process	COI Review Result
★ Haiyan Tong	Principal Investigator	✓	✗ 19-05286	✓		Completed	No Conflict
Hao Chen	Co-investigator	✓	✗ 19-05288	✓		Completed	No Conflict
👤 James Samet	Co-investigator	✓	✗ 19-05278	✓		Completed	No Conflict
Martin Case	Study Coordinator	✓	✗ 19-05280	✓		Completed	No Conflict
Claudia Salazar	Study Coordinator	✓	✗ 19-05284	✓		Completed	No Conflict
Elizabeth Corteselli	Research Assistant	✓	✗ n/a	n/a			n/a

Martha Almond	Other Collaborator	✓	✓	n/a	n/a		n/a
Michael Breen	Other	✓	✗	n/a	n/a		n/a
 Philip Bromberg	Other Collaborator	✓	✓	19-05281	✓	Completed	No Conflict
 Melissa Caughey	Other Collaborator	✓	✓	19-05277	✓	Completed	No Conflict
 Robert Devlin	Other Collaborator	✓	✗	19-05285	✓	Completed	No Conflict
David Diaz-sanchez	Other Collaborator	✓	✗	n/a	n/a		n/a
 Andrew Ghio	Other oncall physician	✓	✗	19-05344	✓	Completed	No Conflict
 Alan Hinderliter	Other Collaborator	✓	✓	19-05279	✓	Completed	No Conflict
Tracey Montilla	Other Nurse	✓	✓	n/a	n/a		n/a
 David Peden	Other Collaborator	✓	✓	19-05283	✓	Yes Completed	No Conflict
Ana Rappold	Other statistics	✓	✗	n/a	n/a		n/a
Wan Shen	Other statistics	✓	✗	n/a	n/a		n/a
Julie Wood	Other Nurse	✓	✗	n/a	n/a		n/a

NOTE: The IRB database will link automatically to [UNC Human Research Ethics Training database](#) and the UNC Conflict of Interest (COI) database. Once the study is certified by the PI, all personnel listed (for whom we have email addresses) will receive separate instructions about COI disclosures. The IRB will communicate with the personnel listed above or the PI if further documentation is required.

3. If this research is based in a center, institute, or department (Administering Department) other than the one listed above for the PI, select here. Be aware that if you do not enter anything here, the PI's home department will be AUTOMATICALLY inserted when you save this page.

Department

Aux Services Affiliates: EPA

3. Funding Sources

1. Is this project funded (or proposed to be funded) by a contract or grant from an organization EXTERNAL to UNC-Chapel Hill?

Yes

Is UNC-CH the **direct** recipient of any Federal funding for this study? You should answer 'yes' *only* if you are the grantee. You should answer 'no' if you are the recipient of a sub-award or contractor under the grant.

No

Funding Source(s) and/or Sponsor(s)

Sponsor Name	UNC Ramses Number	Sponsor Type	Prime Sponsor Name	Prime Sponsor Type	Sponsor/Grant Number	Detail
United States Environmental Protection Agency (EPA)	Currently Not Available	Federal				view

2. Is this study funded by UNC-CH (e.g., department funds, internal pilot grants, trust accounts)?

No

3. Is this research classified (e.g. requires governmental security clearance)?

No

4. Is there a master protocol, grant application, or other proposal supporting this submission (check all that apply)?

- ☒ Grant Application
- ☒ Industry/Federal Sponsor Master Protocol
- ☒ Student Dissertation or Thesis Proposal
- ☒ Investigator Initiated Master Protocol
- ☒ Other Study Protocol

4. Screening Questions

The following questions will help you determine if your project will require IRB review and approval.

[The first question is whether this is RESEARCH \(click for details\)](#)

1. Does your project involve a systematic investigation, including research development, testing and evaluation, which is designed to develop or contribute to generalizable knowledge? PLEASE NOTE: You should only answer yes if your activity meets all the above.

Yes

[The next questions will determine if there are HUMAN SUBJECTS \(click for details\)](#)

2. Will you be obtaining information or biospecimens through intervention or interaction with the individual, and use, study, or analysis of the information or biospecimens? This would include any communication or interpersonal contact between investigator and subject such as using in-person or online questionnaires/surveys, interviews, focus groups, observations, treatment interventions, etc. PLEASE NOTE: Merely obtaining information FROM an individual does not mean you should answer 'Yes,' unless the information is also ABOUT them.

Yes

3. Will you be obtaining, using, studying, analyzing, or generating identifiable private information or identifiable biospecimens collected through means other than direct interaction? This would include data, records or biological specimens that are currently existing or will be collected in the future for purposes other than this proposed research (e.g., medical records, ongoing collection of specimens for a tissue repository).

OR

Will you be using human specimens that are not individually identifiable for [FDA-regulated in vitro diagnostic \(IVD\) device investigations](#)?

Yes

The following questions will help build the remainder of your application.

4. Will subjects be studied in the Clinical and Translational Research Center (CTRC, previously known as the GCRC) or is the CTRC involved in any other way with the study? (If yes, this application will be reviewed by the CTRC and additional data will be collected.)

No

5. Does this study directly recruit participants through the UNC Health Care clinical settings for cancer patients **or** does this study have a focus on cancer or a focus on a risk factor for cancer (e.g. increased physical activity to reduce colon cancer incidence) **or** does this study receive funding from a cancer agency, foundation, or other cancer related group? (If yes, this application may require additional review by the Oncology Protocol Review Committee.)

No

6. Are any personnel, organizations, entities, facilities or locations in addition to UNC-Chapel Hill involved in this research (e.g., is this a multi-site study or does it otherwise involve locations outside UNC-CH, including foreign locations)? You should also click "Yes" if you are requesting reliance on an external IRB, or that UNC's IRB cover another site or individual. [See guidance.](#)

No

Exemptions

Request Exemption

Some research involving human subjects may be eligible for an exemption which would result in fewer application and review requirements. This would not apply in a study that involves drugs or devices, involves greater than minimal risk, or involves medical procedures or deception or minors, except in limited circumstances.

1. Would you like your application evaluated for a possible exemption?

No

Part A. Questions Common to All Studies

A.1. Background and Rationale

- A.1.1. Provide a summary of the background and rationale for this study (i.e., why is the study needed?). If a complete background and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive background and literature review, including references.

Exposure to air pollution, including particulate matter (PM) and ozone, is a well-known risk factor for respiratory/cardiovascular morbidity and mortality worldwide (reviewed in 1-4). Chronic exposure to air pollution may cause systemic and pulmonary oxidative stress and inflammation, leading to endothelial dysfunction, increased blood pressure, decreased heart-rate variability, and cardiovascular disease, resulting in peripheral arterial disease, ischemic events, arrhythmia, and heart failure (reviewed in 5). The WHO estimates that 80% of outdoor air pollution-related deaths are caused by ischemic heart disease and strokes, with the remainder attributed to COPD, respiratory infection, and lung cancer (6).

Omega-3 fatty acids are involved in human physiology, two important associated with beneficial effects being: eicosapentaenoic acid (20:5, n-3; EPA) and docosahexaenoic acid (22:6, n-3; DHA). EPA and DHA are mainly found in seafoods and fish oils. Alpha-linolenic acid (18:3, n-3; ALA) is a substrate for the synthesis of EPA and DHA, but the conversion is inefficient (reviewed in 15). For example, in the plasma, only 0.2% ALA converted to EPA, and less than 1% ALA converted to DHA (14). Thus dietary intake of EPA and DHA is necessary for optimal health.

Dietary consumption of EPA and DHA has been shown to confer protection of the cardiovascular system via a reduction of inflammation (7-10). Our lab (11) and others (12-13) have previously demonstrated that dietary supplementation with fish oil attenuates ambient PM-mediated heart rate variability changes and endothelial dysfunction in middle-aged and elderly adults. However, there is little known about the effects of dietary fish oil supplementation on other air pollutants. In this study, we will correlate EPA and DHA intake and tissue levels with indices of respiratory and cardiovascular health as they are modified by exposure to ambient air pollution.

In this study, healthy 25-55 year-old male and female subjects will be pre-screened for their dietary intake of EPA and DHA. Qualified volunteers will be divided into two groups, group 1: individuals voluntarily taking at least 3 g/wk of EPA and DHA from dietary sources including fish oil supplements and ocean fish/shellfish consumption for a period of at least 6 months prior to enrollment in the study; group 2: individuals who have consumed no more than 1 serving size (4-6 oz)/month of ocean fish/shellfish, or no more than 1 pill/month of fish oil supplement during the 6 month period preceding enrollment. Then volunteers will complete a blood omega-3 index screening. Subjects from group 1 with omega-3 index of approximately 5.5% or higher, and subjects from group 2 with omega-3 index of approximately 4% or lower will be considered for the study. Qualified subjects will come to the EPA Human Studies Facility for up to 5 sessions, each consisting of 2 consecutive visit days. The following endpoints will be taken from subjects: blood pressure, heart rate variability (HRV) measurements, venous blood, brachial artery diameter, retinal venule and arteriole diameter, and spirometry. Air pollution exposure will be assessed for the 24 hour period of each visit using area-specific air quality data interfaced with activity monitoring and GPS-tracked location for each subject. We

hypothesize that dietary consumption of EPA and DHA modifies ambient air pollution induced adverse cardiovascular responses.

1. Chin MT. Basic mechanisms for adverse cardiovascular events associated with air pollution. *Heart*. 2015 Feb;101(4):253-6.
2. Nasser Z, Salameh P, Nasser W, Abou Abbas L, Elias E, Leveque A. Outdoor particulate matter (PM) and associated cardiovascular diseases in the Middle East. *Int J Occup Med Environ Health*. 2015;28(4):641-61.
3. Wang C, Tu Y, Yu Z, Lu R. PM_{2.5} and Cardiovascular Diseases in the Elderly: An Overview. *Int J Environ Res Public Health*. 2015 Jul 16;12(7):8187-97.
4. Kelly FJ, Fussell JC. Linking ambient particulate matter pollution effects with oxidative biology and immune responses. *Ann N Y Acad Sci*. 2015 Mar;1340:84-94.
5. Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol*. 2015 Nov;12(11):627-42.
6. World Health Organization. Ambient (outdoor) air quality and health (online), <http://www.who.int/mediacentre/factsheets/fs313/en/> (access on 2/19/16)
7. Holguin F, Téllez-Rojo MM, Lazo M, Mannino D, Schwartz J, Hernández M, Romieu I. Cardiac autonomic changes associated with fish oil vs soy oil supplementation in the elderly. *Chest*. 2005 Apr;127(4):1102-7.
8. Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival-4. *Cardiovasc Drugs Ther*. 1997 Jul;11(3):485-91.
9. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr*. 1997 May;65(5 Suppl):1645S-1654S.
10. Endres S, von Schacky C. n-3 polyunsaturated fatty acids and human cytokine synthesis. *Curr Opin Lipidol*. 1996 Feb;7(1):48-52.
11. Tong H, Rappold AG, Diaz-Sanchez D, Steck SE, Berntsen J, Cascio WE, Devlin RB, Samet JM. Omega-3 fatty acid supplementation appears to attenuate particulate air pollution-induced cardiac effects and lipid changes in healthy middle-aged adults. *Environ Health Perspect*. 2012 Jul;120(7):952-7.
12. Romieu I, Téllez-Rojo MM, Lazo M, Manzano-Patiño A, Cortez-Lugo M, Julien P, Bélanger MC, Hernandez-Avila M, Holguin F. Omega-3 fatty acid prevents heart rate variability reductions associated with particulate matter. *Am J Respir Crit Care Med*. 2005 Dec 15;172(12):1534-40.
13. Romieu I, Garcia-Esteban R, Sunyer J, Rios C, Alcaraz-Zubeldia M, Velasco SR, Holguin F. The effect of supplementation with omega-3 polyunsaturated fatty acids on markers of oxidative stress in elderly exposed to PM_{2.5}. *Environ Health Perspect*. 2008 Sep;116(9):1237-42.
14. Pawlosky RJ, Hibbeln JR, Novotny JA, Salem N Jr. Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. *J Lipid Res*. 2001 Aug;42(8):1257-65.
15. Burdge GC, Calder PC. Dietary alpha-linolenic acid and health-related outcomes: a metabolic perspective. *Nutr Res Rev*. 2006 Jun;19(1):26-52.

A.1.2. State the research question(s) (i.e., specific study aims and/or hypotheses).

We hypothesize that dietary intake of DHA and EPA modifies ambient air pollution induced adverse cardiovascular responses.

A.2. Subjects

A.2.1. Total number of subjects proposed across all sites by all investigators (provide exact number; if unlimited, enter 9999):

100

A.2.2. Total number of subjects to be studied by the UNC-CH investigator(s) (provide exact number; if unlimited, enter 9999):

100

A.2.3. If the above numbers include multiple groups, cohorts, or ranges or are dependent on unknown factors, or need any explanation, describe here:

Subjects for this study will be healthy 25-55 year-old male and female subjects. Our recruitment goal is for 60 subjects to complete this study protocol. Subjects will be recruited by FEFA Inc (see recruitment section).

A.2.4. Do you plan to enroll subjects from these vulnerable or select populations:
If you will include children, prisoners or nonviable neonates or neonates of uncertain viability, please check the appropriate category below and complete the additional sections.

You should check "Pregnant women" if you specifically intend to recruit women who are pregnant or are not excluding pregnant women in biomedical research that is greater than minimal risk. Do not check if you are conducting a survey of the general public or conducting secondary data analysis or chart review not aimed at pregnant women.

Only check UNC-CH Student athletes, athletic teams, or coaches if you have specific plans to enroll these subjects. This is not applicable for intramural or club sports. For definitions and guidance see SOP 1201: Vulnerable subjects in research.

☒ Children (under the age of majority for their location)

Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.

☒ Pregnant women

☒ Nonviable neonates or neonates of uncertain viability

☒ Prisoners, others involuntarily detained or incarcerated (this includes parolees held in treatment centers as a condition of their parole)

If an enrolled participant becomes incarcerated during the course of the research, they must be removed from the research project until such time as the IRB (and OHRP for NIH funded projects) approves the study to include prisoners, unless there is an immediate risk to the participant from ending treatments under the protocol.

☒ UNC-CH Student athletes, athletic teams, or coaches

A.2.5. Based on your recruitment plan and target sample population, are you likely to include any of the following as subjects? Select all that apply. This is not applicable to secondary data analysis or chart review.

Based on your responses, the consent form builder will insert the required text into your consent form template.

☒ Decisionally impaired individuals

(e.g., Mini mental state examination (MMSE), Montreal cognitive assessment (MOCA))

☒ Children who are wards of the State (Foster children)

☒ Non-English-speaking individuals

☒ UNC-CH Students

☒ UNC-CH Employees

☒ People, including children, who are likely to be involved in abusive relationships, either as perpetrator or victim.

This would include studies that might uncover or expose child, elder or domestic abuse/neglect. ([See SOP Appendix A](#))

A.2.6. If any of the above populations are checked (excluding 'Decisionally impaired individuals' and 'Children who are wards of the State (Foster children)'), please describe your plans to provide additional protections for these subjects.

No Answer Provided

A.2.7. Age range of subjects:

Minimum age of subject enrolled	25
	years
Maximum age of subject enrolled	55
» If no maximum age limit, indicate 99	
	years

A.3. Inclusion/exclusion criteria

A.3.1. List required characteristics of potential subjects (i.e., inclusion and exclusion criteria). If not covered, list also characteristics that would preclude their involvement.

1. Aged 25-55 years old healthy male and female (19?BMI?35).
2. Normal resting ECG. No history of heart arrhythmia.
3. Oxygen saturation greater than 96% at the time of physical exam.
4. Taking at least 3 grams of EPA and DHA from dietary sources including fish oil supplements and ocean fish/shellfish for a 6 months or longer period of time preceding enrollment in the study, and with a blood omega-3 index of approximately 5.5% or high; or taking no more than 1 serving size (4-6 oz)/month of ocean fish/shellfish, or no more than 1 pill/month of fish oil supplement during the previous 6 months or longer period of time, and with a blood omega-3 index of approximately 4% or lower.

A.3.2. Justify any exclusion based on race, gender or ethnicity

1. Individuals with a history of acute or chronic cardiovascular disease, such as myocardial infarction.
2. Individuals with a history of chronic respiratory disease, such as COPD or have been diagnosed by physician with persist moderate to severe asthma.
3. Individuals with a history of cancer (possible exception for history of non-melanoma skin cancer).
4. Uncontrolled hypertension (?150 systolic, ?90 diastolic).
5. Individuals who are diabetic (previously diagnosed or with hemoglobin A1c level >6.4%).
6. Individuals who are currently smoking (including vaping, or using hookah or e-cigarettes) or have a smoking history within 1 year of study (defined as more than 1 pk/yr in the past year) or have a greater than/equal to a 5 pack year smoking history.
7. Individuals living with a smoker who smokes inside the house.
8. Individuals who are regularly exposed to high levels of vapors, dust, gases, or fumes.
9. Individuals who do not understand or speak English.
10. Individuals who are taking b-blocker medications.
11. Individuals who are taking statins.
12. Individuals that are unwilling or unable to maintain their current dietary and medication pattern for the whole study.
13. Individuals with bleeding or clotting disorders.
14. Individuals who have active allergies.
15. Individuals who have skin allergy to tape or electrodes.
16. Individuals who are pregnant or attempting to become pregnant.
17. Individuals who have unspecified illnesses, which in the judgment of the investigators might increase the risk associated with clinical procedures will be a basis for exclusion.

Temporary exclusion criteria:

1. Individuals who have had recent (within 6 months) abdominal and/or eye surgery, or been diagnosed with any type of hernia, as well as any other contraindications for raised intra-abdominal pressure.
2. Individuals who have had an acute respiratory illness within 2 weeks.

Use of other medications will be evaluated on a case-by-case basis. There is the potential that an individual's current medication use will preclude them from participating in the study at the current time, but they may be reassessed and potentially rescheduled for participation at a later time.

A.3.3. Will pregnant women or women who become pregnant be excluded?

Yes

If yes, provide justification and describe the type and timing of pregnancy testing to be used:

A pregnancy test will be administered at the first day of each session to any female subject who has child-bearing potential.

A.4. Study design, methods and procedures

Your response to the next question will help determine what further questions you will be asked in the following sections.

A.4.1. Will you be using any **methods or procedures commonly used in biomedical or clinical research** (this would include but not be limited to drawing blood, performing lab tests or biological monitoring, conducting physical exams, administering drugs, or conducting a clinical trial)?

Yes

A.4.2. Describe the study design. List and describe study procedures, including a sequential description of what subjects will be asked to do, when relevant.

This is an observational study. Healthy 25-55 year-old male and female subjects will be pre-screened for their dietary intake of EPA and DHA. Qualified volunteers will be divided into two groups, group 1: individuals voluntarily taking at least 3 g/wk of EPA and DHA from dietary sources including fish oil supplements and ocean fish/shellfish consumption for a period of at least 6 months prior to enrollment in the study; group 2: individuals who have consumed no more than 1 serving size (4-6 oz)/month of ocean fish/shellfish, or no more than 1 pill/month of fish oil supplement during the 6 month period preceding enrollment. Then volunteers will complete a blood omega-3 index screening. Subjects from group 1 with omega-3 index of approximately 5.5% or higher, and subjects from group 2 with omega-3 index of approximately 4% or lower will be considered for the study. We will use the omega-3 index results from IRB Study 15-2960 to determine eligibility when available and with the subject's consent. Qualified subjects will come to the EPA Human Studies Facility for up to 5 sessions, each consisting of 2 consecutive visit days. The following endpoints will be taken from subjects: blood pressure, heart rate variability (HRV) measurements, venous blood, brachial artery diameter, retinal venule and arteriole diameter, and spirometry. Air pollution exposure will be assessed for the 24 hour period of each visit using area-specific air quality data interfaced with activity monitoring, GPS-tracked location, Hexoskin and TrackMyAir data for each subject.

Recruitment

Subjects will be recruited by FEFA Inc (IRB approved protocol 95-EPA-66, see recruitment section). During an initial telephone interview, the subjects will receive information regarding the study and their eligibility will be assessed based on their answers to the scripted questions (Form PCS-0 and Telephone Screening Sheet, included in recruitment materials). A Registered Dietitian may assist with this process via phone interview. Subjects who meet the criteria of the study will be coming for a visit to complete a dietary assessment focused on their consumption of DHA and EPA (Form PCS-6). This assessment questionnaire includes subjects' dietary intake of fish oil supplements, ocean fish/shellfish, and omega-3 fortified foods over the past 6 months. Volunteers will also be tested the blood level of EPA and DHA fatty acids by using a commercially available omega-3 index measurement kit (purchased from OmegaQuant). Blood level of omega-3 index of approximately 4% or lower, or approximately 5.5% or higher will be scheduled for an appointment in the medical station in the U.S. EPA Human Studies Facility for a physical exam.

Physical Exam Day

On the physical exam day, subjects will visit the medical station in the U.S. EPA Human Studies Facility for physical examination by a licensed physician (IRB approved protocol 95-MED-6).

Study sessions 1-5:

Volunteers who are determined eligible to participate in the study will be scheduled for up to 5 – two day visits sessions. Each subject will be scheduled to visit with at least one week interval between two sessions.

We will contact subjects a few days prior to remind them of their scheduled visits. Subjects will be required to avoid 1) alcohol and exposure to a high level of vapors, dust, gases or fumes 24 hours before all visits, and 2) coffee and caffeinated beverages 12 hours before all visits. They will also be required not to eat greasy or high fat content food for 12 hours before the 2nd visit day for all study sessions. A list of Low Fat Breakfast and Lunch Choices (Form FCS-11) will be provided.

On the first visit day of the first study session (day 1, session 1), qualified study volunteers will be counseled and will provide their informed consent to participate in the study. The following consent forms will be used in this study: 1) Consent to Participate in a Research Study (Form PCS-1), 2) Consent for Storing Biological Specimens with Identifying Information (Form PCS-2), 3) Consent to Re-Contact Following Removal from the Study (Form PCS-3), 4) Consent for Genotyping with Identifying Information (Form PCS-4), 5) Consent Checklist (Form PCS-5). Subjects will be given the opportunity to have any questions answered before signing the study consent forms.

Subjects will complete a Residence and Participant Survey (Form PCS-9) to estimate pollutant exposures in their home based on their description of the characteristics of their home (year of construction, materials, etc) and the TrackMyAir application. They will also be asked to complete a baseline dietary food frequency questionnaire (Diet History Questionnaire II). The Dietary History Questionnaire II is developed by the NIH National Cancer Institute Division of Cancer Control and Population Sciences. It is an online version, assessing dietary intake within the last 12 months based on U.S. foods. Subjects will have multiple opportunities to login to the website and complete the questionnaire before the second study session. Form PCS-13 is a hard copy of the questionnaire. While the subject is at HSF, a brief dietary training including online Dietary History Questionnaire (Form PCS-12) and portion size (Form PCS-8) will be provided to help with the completion of the questionnaire. The dietary information will be used for post-study analysis only. Participants will also undergo training for spirometry if necessary. Those subjects who had the spirometry done well from previous studies or from physical exam do not have repeat this procedure. Subjects will also be given a Hexoskin compression shirt to wear overnight that calculates subject ventilation. This consent and training process should add approximately 2 hours to the 1st visit day of the 1st study session.

The following activities will occur on the first session and the following study sessions.

1st visit day:

Upon arrival, the subject's vital signs will be checked. A urine sample will be collected from any female subject who has child-bearing potential.

1. **Heart rate variability (HRV) measurements:** Electrodes for HRV measurement will be placed by an experienced study personnel. The skin in the areas of electrode placement will be cleaned and shaved (if necessary) to ensure that the electrodes will remain securely attached. These electrodes will be connected to a Holter monitor. At the end of day, the Holter monitor will be removed, and the electrodes will be remained for the next day measurement.
2. **24 h dietary recall** (Form PCS-7): On the 1st visit day of the 2nd, 3rd, 4th and 5th study session, a questionnaire will be administrated to subjects to confirm their compliance with their dietary routine. This is a quantitative research method used in nutritional assessment, which asks individuals to recall foods and beverages they consumed in the 24 hours window prior to the interview day.
3. **GPS travel recorder:** A GPS-enabled device will be issued to subjects on the first day of the visit, and returned to the Human Studies Facility on the next day. This device continuously monitors GPS coordinates and records internally. Data is not displayed and is only available to download with proprietary software. The subjects will carry the recorder with them at all times to determine their exposure to air pollution occurs over 24 hr period. Data will be downloaded and stored onto a secure database.
4. **Activity monitor:** An accelerometer-equipped device will be issued to subjects on the first day of the visit, and collected at the facility on the next day. This device measures the level of physical exertion and this measurement can be useful in estimating exposure over a given time period. The subjects will wear the activity monitor over 24 hr period.
5. **Hexoskin:** We will apply a dual-band plethysmography device, which is integrated within a

compression shirt, called Hexoskin, to determine each study participant's daily inhaled dose of ambient PM_{2.5} and ozone, which will be used for the epidemiological analysis. The Hexoskin device consists of: (1) inductive plethysmography consisting of two chest bands (one thoracic band, and one abdominal band), and (2) a small removable recording device that has no display and is kept in the shirt's pocket. The measured displacement of the chest bands will be used to determine minute ventilation (volume of air inhaled per minute). To calculate inhaled dose, the minute ventilation will be combined with PM_{2.5} and ozone exposures, which are determined using EPA's previously developed and evaluated Exposure Model for Individuals (EMI).^{1,2} The inhaled dose will account for participant-specific respiratory ventilations.

A Hexoskin shirt will be issued to the study participants on the 1st day of the visit and returned to the Human Studies Facility on the next day. The size of the shirt for each participant will be determined using tape measurement when they stand up straight. For men, the circumference of the thorax just below the pectoral muscles, and the circumference at the navel line will be measured after a full exhalation. For women, the circumference of the thorax just below the breasts, and the circumference at the navel line will be measured after a full exhalation. The men's and women's size charts, (see Hexoskin SOP) will then be used to determine the men's and women's shirt size, respectively. The breathing sensors on the Hexoskin shirts will measure continuous displacement of the chest bands for each inhalation to determine minute ventilation (volume of air inhaled per minute). The breathing sensors in the Hexoskin shirts will be calibrated using the pneumotach to true measure the minute ventilation while the subjects perform different physical activities for 3-min durations (e.g. sitting or walking on treadmill at 3 mph, 2% elevation).

The shirt will be worn by the study participants for 1 day (24 hours), which starts and ends on the two consecutive days when the participant visits the EPA human studies facility in Chapel Hill, NC. On day 2, EPA clinicians or researchers will download the data from the recording device via a USB cable connection, store the data on a secure EPA desktop computer, and erase the data from the recording device.

6. **TrackMyAir:** We will apply a recently developed EPA smartphone application, called TracMyAir, to determine each study participant's daily (24-h average) ambient PM_{2.5} and ozone exposure and inhaled dose, which will be used for the epidemiological analysis. TracMyAir uses measurements from the official local air quality monitors and input data on home building characteristics, home operating conditions, time-spent in different outdoor and indoor microenvironments, and time-spent at different physical activity levels. TracMyAir uses EPA's previously developed and evaluated Exposure Model for Individuals (EMI).^{1,2} The App accounts for daily variability of house-specific air exchange rates; building-specific infiltration factors for ambient PM_{2.5} and ozone; time spent outdoors, in-vehicles, and indoors at home, work, school, and other; and participant-specific respiratory ventilations.

The TracMyAir App will be used by the EPA clinicians or researchers on days when study participants visit the EPA health study facility. The App will not be installed on participant phones or used by participants. The EPA clinicians will enter the App input data (shown below) for each study participant, and then run the calculation of the daily exposures and doses (approx. 15 s execution time). For each run, the App calculates daily 24-h average exposure and dose for the previous 4 days, which allows for a lag analysis. The exposures and doses will be transferred and stored on a secure EPA desktop computer for subsequent epidemiological analysis by EPA researchers. TracMyAir does not save the calculated exposures and doses on the smartphone.

Input Data from Participants

Home characteristics: floor area, year built, number of floors, type of house (single, multi-family), wind sheltering

Home operating conditions: indoor temperature, open windows (number of windows, opening height, duration), window fans (number of fans, duration, airflow), air cleaners (number of air cleaners, duration),

Microenvironments: daily time spent in 6 microenvironments (outdoors, inside vehicles, indoors at work, school, home, other buildings)

Physical activities: daily time spent at 3 activity levels (sedentary, light, moderate, vigorous)

Demographics: gender, age, body weight, height

2nd visit day:

The subject's vital signs will be checked upon their arrival. GPS travel recorder and activity monitor will be collected. A Daily Follow-up Questionnaire (Form PCS-10) regarding their exposure over the past 24 hours

will be filled by the subject. The following clinical measurements will be conducted:

1. **HRV measurements:** The subjects will be allowed to relax for 20 minutes in a reclined position, after which a 10-minute of resting HRV data will be collected. Measurements of heart rate variability, arrhythmia frequency and complexity, QT-RR interval, and principal component of the T-wave will be performed.
2. **Brachial artery ultrasound (BAU):** Baseline and flow-mediated dilation of the brachial artery will be assessed in the facility using an Acuson Sequoia using a 15 MHz probe ultrasound instrument. The diameter of the brachial artery will be measured at baseline and during reactive hyperemia. The subject will lie supine in subdued light, and blood pressure will be measured 3 times after HRV measurement. A pneumatic tourniquet will be placed around the right lower arm proximal to the target artery. Gated baseline images of the brachial artery will be acquired. The pneumatic cuff will then be inflated to a pressure of 50 mm Hg above the systolic pressure for 5 minutes, and increased flow will be induced by sudden cuff deflation. A second scan will be performed following deflation. Images of the brachial artery will be acquired and stored on a personal computer, and subsequently analyzed using a semi-automated offline quantification system.
3. **Retinal image:** An FDA-approved, commercially available, non-mydratic fundus camera (Canon CR-2) will be used. Images will be taken from both eyes, and may have to be repeated (up to 3 times per eye per session) as needed for optimal image quality (i.e., to correct for poor focus, contrast, brightness) caused by the subject moving or blinking during image acquisition. No dilation of the pupils will be required. Glasses or contacts have to be removed for this procedure.
4. **Venous blood samples:** Approximately 60 ml of blood sample will be collected from an antecubital site. The total blood draw will be approximately 250 ml for the entire study (at least 5 week long). Blood will be analyzed for, but not limited to, phospholipids, CBC, and lipid panel. A portion of the blood sample will be used for DNA isolation and genotyping with the subject's explicit permission. Consent to genotyping is not a requirement for enrollment in the study. The glutathione S-transferase mu 1 (GSTM1) is of interest in this study, because recent reports have shown that individuals with the GSTM1 null genotype are more susceptible to air pollutants. The GSTM1 gene plays an important role in the response to respiratory oxidative stress and inflammation. Present evidence suggests that the GSTM1 null genotype is highly prevalent in the population, and associated with increased risk of asthma incidents among children, and the development of chronic obstructive pulmonary disease (COPD) in adults, when these populations are exposed to environmental tobacco smoke or secondhand smoke, ambient air pollutants such as ozone and diesel exhaust particles, or endotoxin and other pathogen-associated particles. The purpose of the genotyping is to identify GSTM1 sufficient and GSTM1 null individuals, but this information will not be utilized to screen the subjects. Rather, data will be analyzed at the end of the study to determine whether GSTM1 genotype influenced the cardiovascular and pulmonary effects to ambient air pollution in subjects with high and low levels of EPA/DHA intake.
5. **Spirometry:** will be taken to assess pulmonary function by measuring the volume of air that is exhaled and the rate of airflow during exhalation after a maximal inhalation. The subjects will inhale as deeply as possible, then exhale as rapidly and completely as possible into the spirometer.
6. **GPS travel recorder:** This device continuously monitors GPS coordinates and records internally. Data is not displayed and is only available to download with proper proprietary software. The subjects will carry the recorder with them at all times to determine their level of exposure to air pollution during the 24 hour period. Data will be downloaded and stored onto a secure database. A follow-up questionnaire will be collected before they leave.
7. **Activity monitor:** The subjects will wear the activity monitor during the 24 hr period. This device measures the level of physical exertion and this measurement will be used to estimate ventilatory rate to calculate exposure over a given time period. Data will be downloaded and stored onto a secure database.
8. **Exposure assessment:** will be conducted outside the presence of the subject. We will evaluate daily measurements of, PM2.5, ozone, SO₂, NO₂ and CO by obtaining data from air monitoring stations located in Raleigh and Durham. Based on GPS travel and activity data, a computer-based air pollution model will be used to predict the level of air pollution inhaled by the subjects during the study.

In this study, our primary endpoints will be measurements of heart rate variability and blood biomarkers. Our secondary endpoints will be endothelial cell function from BAU measurements, diameters of retinal arteries and veins, and pulmonary function indices.

9. **TrackMyAir:** We will apply a recently developed EPA smartphone application, called TracMyAir, to

determine each study participant's daily (24-h average) ambient PM_{2.5} and ozone exposure and inhaled dose, which will be used for the epidemiological analysis. TracMyAir uses measurements from the official local air quality monitors and input data on home building characteristics, home operating conditions, time-spent in different outdoor and indoor microenvironments, and time-spent at different physical activity levels. TracMyAir uses EPA's previously developed and evaluated Exposure Model for Individuals (EMI).^{1,2} The App accounts for daily variability of house-specific air exchange rates; building-specific infiltration factors for ambient PM_{2.5} and ozone; time spent outdoors, in-vehicles, and indoors at home, work, school, and other; and participant-specific respiratory ventilations.

The TracMyAir App will be used by the EPA clinicians or researchers on days when study participants visit the EPA health study facility. The App will not be installed on participant phones or used by participants. The EPA clinicians will enter the App input data (shown below) for each study participant, and then run the calculation of the daily exposures and doses (approx. 15 s execution time). For each run, the App calculates daily 24-h average exposure and dose for the previous 4 days, which allows for a lag analysis. The exposures and doses will be transferred and stored on a secure EPA desktop computer for subsequent epidemiological analysis by EPA researchers. TracMyAir does not save the calculated exposures and doses on the smartphone.

Input Data from Participants

Home characteristics: floor area, year built, number of floors, type of house (single, multi-family), wind sheltering

Home operating conditions: indoor temperature, open windows (number of windows, opening height, duration), window fans (number of fans, duration, airflow), air cleaners (number of air cleaners, duration),

Microenvironments: daily time spent in 6 microenvironments (outdoors, inside vehicles, indoors at work, school, home, other buildings)

Physical activities: daily time spent at 3 activity levels (sedentary, light, moderate, vigorous)

Demographics: gender, age, body weight, height

A.4.3. If subjects are assigned or randomized to study "arms" or groups, describe how they are assigned.

- Describe the methods of computing the randomization schedule (if any) and maintaining blinding (if any).
- Who will perform these computations?
- How will you verify each subject's eligibility prior to randomization?

This is not a randomized study. Healthy 25-55 year-old male and female subjects will be pre-screened for their dietary intake of EPA and DHA, and will be divided into two groups, group 1: individuals voluntarily taking at least 3 g/wk of EPA and DHA from dietary sources including fish oil supplements and ocean fish/shellfish consumption for a period of at least 6 months prior to enrollment in the study; group 2: individuals who have consumed no more than 1 serving size (4-6 oz)/month of ocean fish/shellfish, or no more than 1 pill/month of fish oil supplement during the 6 month period preceding enrollment. Then volunteers will complete a blood omega-3 index screening. Subjects from group 1 with omega-3 index of approximately 5.5% or higher, and subjects from group 2 with omega-3 index of approximately 4% or lower will be considered for the study.

A.4.4. Describe any follow up procedures.

This is an observational study, and will have no follow-up procedures beyond those undertaken during participation in the study.

A.4.5. Once this study has been approved by the IRB, for how many months or years will this study be active (you are collecting data or have access to identifiers)?

It is anticipated that the duration of this study will be approximately 1 year. Subject recruitment and screening

is expected to be continuous throughout the study until the intended number of subjects is reached. Scheduling constraints imposed by concurrent studies in the U.S. EPA Human Studies Facility are expected to limit the rate at which subjects can be enrolled to approximately 1-4 subjects per week.

A.4.6. Will this study use any of the following methods?

- | |
|---|
| <input checked="" type="checkbox"/> Audio Recording |
| <input checked="" type="checkbox"/> Video Recording |
| <input checked="" type="checkbox"/> Behavioral observation - (e.g., Participant, naturalistic, experimental, and other observational methods typically used in social science research) |
| <input checked="" type="checkbox"/> Pencil and paper questionnaires or surveys |
| <input checked="" type="checkbox"/> Electronic questionnaires or surveys |
| <input checked="" type="checkbox"/> Telephone questionnaires or surveys |
| <input checked="" type="checkbox"/> Interview questionnaires or surveys |
| <input checked="" type="checkbox"/> Other questionnaires or surveys |
| <input checked="" type="checkbox"/> Focus groups |
| <input checked="" type="checkbox"/> Diaries or journals |
| <input checked="" type="checkbox"/> Photovoice |
| <input checked="" type="checkbox"/> Still photography |

A.4.7. If there are procedures or methods that require specialized training, describe who (role/qualifications) will be involved and how they will be trained.

Spirometry will be performed by a qualified researcher with experience in both clinical and research duties.

Venipuncture will be performed by an experienced study personnel.

Placement of the ECG electrodes will be done by an experienced study personnel.

Heart rate variability will be collected by a qualified researcher with experience in both clinical and research duties.

Holter monitor data download will be performed within 24 hours following the current study visit, and will be assessed by a Registered Nurse or an experienced research personnel.

Brachial artery ultrasound will be performed by a trained researcher or research assistant.

Retinal Imaging will be performed by a trained researcher or research assistant.

Dietary phone screening, assessment questionnaire for dietary EPA and DHA consumption, portion size training, dietary food frequency questionnaire (Dietary History Questionnaire II), 24 hour recall, TrackMyAir and Hexoskin will be administered and instructed by a trained researcher.

A.4.8. Are there cultural issues, concerns or implications for the methods to be used with this study population?

No

A.4.A. Biomedical methods and procedures

A.4.A.1. Is this an interventional study?

No

Distinguish what is being done specifically for this research from procedures that would be done anyway for clinical care:

All procedures listed in this protocol are specifically for research purpose, however, they can be also found in clinical settings. We will perform routine clinical procedures including measuring blood pressure and collecting venous blood, as well as specialized clinical procedures, such as measuring heart rate variability, assessing brachial artery diameter and retinal venule and arteriole diameter, and using spirometry to evaluate lung function.

A.4.A.2. Is this a Clinical Study?

Check YES if this study involves research using human volunteers that is intended to add to medical knowledge. There are two main types of clinical studies: clinical trials and observational studies. Do NOT check yes merely because you are conducting research in a clinical setting or using clinical data.

[Click here for additional definition of "Clinical Study"](#)

Yes

Will this clinical trial be listed in [ClinicalTrials.gov](https://clinicaltrials.gov), either by you or the sponsor?

Yes

Choose the appropriate Phase designation for this clinical trial.

☒ Pilot Study

☒ Phase I

☒ Phase I/II

☒ Phase II

☒ Phase III

☒ Phase IV

☒ Other

A.4.A.3. If the study involves the use of placebo control, provide justification

No Answer Provided

A.4.A.4. Will this study involve drugs, biologics or other substances (such as a botanical or dietary supplement)?

For guidance on dietary supplements, see Section VI, C [FDA guidance document UCM229175.pdf](#)

No

A.4.A.5. Is there an Investigational New Drug application (IND) for this study?

No

Please check below:

☒ This study does not involve drugs, biologics or other substances.

☒ I am using a U.S. commercially available agent, consistent with labeling.

☒ I am studying a botanical substance or dietary supplement intended to affect the structure and/or function of the body; it is **not** intended to cure, treat, mitigate, prevent or diagnose disease, including its associated symptoms.

A.4.A.6. When the intent of a clinical investigation is to collect information about the safety or effectiveness of a device, the need for an Investigational Device Exemption (IDE) must be evaluated. Please review the [Investigational Device Guidance](#) document prior to completing this section. Your response to the following questions will determine if an IDE is needed.

A. Select the response that best describes your investigation:

4. The device(s) in this research is being **used as "tool"** to address a research question, collect information or test a physiologic principle. No data is collected about the device itself.

Upload information about the device in the Attachments section. Include device description, brochures, illustrations, operating or procedural manuals, instructions/directions and anything else that may be helpful to the IRB in conducting a risk/benefit analysis.

A.4.A.7. Does your study involve any of the following? (check all that apply)

✗ Embryonic stem cells

✗ Fetal tissue

✓ Genetic testing (see [GINA](#) and [GWAS](#))

✓ Clinical laboratory tests

If McLendon Labs will do the testing, you must complete the appropriate form found at [UNC Health Care](#) and submit to them for review.

✗ Testing for communicable diseases that have mandated reporting requirements ([link to state guidance](#))

✓ Point of Care Testing (POCT), which is CLIA-approved testing done at the "bedside" or site of care by hospital or clinic personnel (not by subject). Examples include urine pregnancy testing, glucose monitoring, etc.

If McLendon Labs will do the testing, you must complete the POCT form found at [UNC Health Care](#) and submit to them for review.

✗ If your study utilizes **radiopharmaceuticals** to address basic science questions, an IND is not necessary.

Instead, your study will be reviewed/approved by the [Radioactive Drug Research Committee](#) (RDRC); approval by the Radiation Safety Subcommittee (RSS) is not required.

If you have questions about the RDRC approval process, please contact [Dede Corvinus](#).

✗ Diagnostic or therapeutic ionizing radiation, or radioactive isotopes (not covered under [21 CFR 361.1](#)), which subjects would not receive otherwise if not participating in this research study. Do not check if all radiation is administered as standard of care. Do check if your study includes [views/scans that represent no greater than minimal risk as determined by the Radiation Safety Sub-committee. Application for Human Use of Radiation in Research.](#)

✗ Gadolinium administered as a contrast agent

✗ Recombinant DNA or gene transfer to human subjects

✗ Any research activities conducted in the UNCHC Perioperative areas. This includes Pre-care, Pre-op, Operating room and PACU.

You must complete the [Checklist for Perioperative Services](#) and return it to moe_lim@med.unc.edu

✗ Any form of medical imaging (ultrasound, MRI, CT, X-ray, PET-CT, PET-MRI)

A.4.A.8. Will your study involve storage of specimens for future unspecified research?

Yes

Please explain:

Separate storage consent form will be included.

Will any personal identifiers or codes be retained with the specimens that would allow anyone to link the specimen back to an individual subject?

Yes

A.5. Benefits to subjects and/or society

A.5.1. Describe how this study will contribute to generalizable knowledge that will benefit society.

For society, this study will provide new information on the effects of consumption of dietary fatty acids (specifically EPA and DHA) on the cardiovascular system, lung function, and systemic inflammation under exposure to ambient air pollution. Data from this study will help the US EPA better understand the relationship between air pollution and cardiopulmonary morbidity and mortality so that ambient air quality standards can be properly set. Findings from this study will also have the potential to contribute to devising effective dietary strategies aimed at protecting millions from the untoward effects of exposure to air pollution.

A.5.2. Does this study have the potential for direct benefit to individual subjects in this study?

No

Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form, if there is a consent form. Do not cite monetary payment or other compensation as a benefit.

Explain

Subjects will receive no direct benefit from participating in this study other than receiving a medical examination, including blood work, brachial artery ultrasound, spirometry, and an ECG measurement. Subjects will have full access to these records. They will also gain knowledge about the health effects of ambient air pollution and whether dietary intake of EPA and DHA might protect them from air pollutants.

A.5.3. Are there plans to communicate the results of the research OR results of any clinical tests administered for the research back to the subjects?

No

A.6. Risks and measures to minimize risks

For each of the following categories of risk you will be asked to describe any items checked and what will be done to minimize the risks.

A.6.1. Psychological

- ☒ Emotional distress
- ☒ Embarrassment
- ☒ Consequences of breach of confidentiality (Check and describe only once on this page)
- ☒ Other

A.6.2. Describe any potential psychological risks checked above and what will be done to minimize these risks

There is a possibility that participants may feel embarrassed about their answers on their dietary questionnaire or TracMyAir app. The subjects will be told that these are research tools only. Results will not be revealed to anyone outside the researcher team on the protocol.

A.6.3. Social

- ☒ Loss of reputation or standing within the community
- ☒ Harms to a larger group or community beyond the subjects of the study (e.g., stigmatization)
- ☒ Consequences of breach of confidentiality (Check and describe only once on this page)
- ☒ Other

A.6.4. Describe any potential social risks checked above and what will be done to minimize these risks

Risk of breach of confidentiality is minimal. All subjects will be assigned a study number which will be used for data recording – in place of the subject's name. The study number is all that will be entered into computer databases. All paper files that may contain the subject's name or screening number are secure in the EPA building that has limited access 24 hours/day. Any abnormal medical findings (CBC, ECG, brachial artery ultrasound image, retinal image, spirometry) will be discussed with the volunteer and the volunteer will be counseled to seek treatment from his/her personal physician if indicated at his/her own expense. All samples will be stored at the U.S. EPA HSF. A numeric coding system will be used to ensure that subjects cannot be directly identified from the samples alone.

A.6.5. Economic

- ☒ Loss of income
- ☒ Loss of employment or insurability
- ☒ Loss of professional standing or reputation
- ☒ Loss of standing within the community
- ☒ Consequences of breach of confidentiality (Check and describe only once on this page)
- ☒ Other

A.6.6. Describe any potential economic risks checked above and what will be done to minimize these risks.

No Answer Provided

A.6.7. Legal

- ☒ Disclosure of illegal activity
- ☒ Disclosure of negligence
- ☒ Consequences of breach of confidentiality (Check and describe only once on this page)
- ☒ Other

A.6.8. Describe any potential legal risks checked above and what will be done to minimize these risks

No Answer Provided

A.6.9. Physical

- ☒ Medication side effects
- ☒ Pain
- ☒ Discomfort
- ☒ Injury
- ☒ To a nursing child or a fetus (either through mother or father)

A.6.10. Describe any potential physical risks checked above, including the category of likelihood and severity, and what will be done to minimize these risks. Where possible, describe the likelihood of the risks occurring, using the following terms:

- Very Common (approximate incidence > 50%)
- Common (approximate incidence > 25 - 50%)
- Likely (approximate incidence of > 10 - 25%)
- Infrequent (approximate incidence of > 1 - 10%)
- Rare (approximate incidence < 1%)

Describe severity of risks using the following grading scale:

- Mild- No disruption to the subject's ability to perform daily activities; may include non-prescription intervention only
- Moderate- Temporary interference with daily activities; may include prescription intervention
- Severe- Interference with daily activities; medically significant but not life threatening
- Life threatening

Examples:

Rare (< 1%) and Severe: blindness

Rare (< 1%) and Mild: dry skin, dry mouth, transient headache

If you are using these terms differently than described above, please provide your study-specific definitions.

Phase 1 trials: Due to limited experience, incidence may be better described as the number of events that have occurred in the total number of animals/humans studied.

General measures to minimize the risks: Medical screening of the potential subjects is designed to exclude those that may be at risk from the study procedures. A physician is available by pager whenever a subject is undergoing any procedure in the US EPA Human Studies Facility. The physician will evaluate the patient as

needed. US EPA Human Studies Facility has a well-equipped medical station and the University of North Carolina Hospital is within a short distance. Subjects will be urged to contact the medical station or the physician should they experience any abnormal symptoms or discomfort after they leave. Risks associated with specific study procedures are as follows:

Pulmonary function tests (spirometry) are standard non-invasive techniques that are commonly used in studies of pulmonary function on populations of all ages and entail little or no risk to the subject. In rare circumstances subjects could become dizzy from performing spirometric measurements.

ECG and heart rate variability are standard non-invasive techniques commonly used for heart rate and rhythm analysis and entail little or no risk to the subject. Infrequently, there is the possibility that preparation of the skin for electrode placement and removal may cause temporary minor skin redness or irritation. Itching, burning, or soreness might occur in some subjects. It is also possible for discoloration from the tape area to occur. If these symptoms persist or worsen, the subject will be told to contact the medical station immediately.

Retinal image is considered non-invasive, with the most likely side-effect being momentary visual impairment caused by the firing of the flash used by the camera. This would be considered very common.

Brachial artery ultrasound: There are no known risks associated with imaging of the brachial artery. However, intermittent brief occlusion of blood flow to the forearm may cause mild discomfort and temporary sensations such as tingling and numbness until the blood pressure cuff is released (very common). Approximately 0.5 % of participants develop painless petechiae in the arm which is examined and these resolve within a few days (rare).

Venipuncture will be done by insertion of the needle and may cause minor discomfort at the site of injection and there is a possibility that a bruise will form which may be painful for 2-3 days. It is possible that the subject may feel light-headed or even faint due to anxiety about the blood draw. Rarely, a skin infection may occur. To minimize these risks, blood is drawn by an experienced study personnel at the medical station. Subjects will be in a reclined position and closely monitored for any signs of faintness, given liquids and food to eat if requested, and only allowed to leave the facility after a 15-minute waiting period to make sure they are stable.

Consumption of EPA and DHA: Omega-3 fatty acids are essential factors in the human diet. Consumption of 0.5 g/d of EPA and DHA is recommended for cardiovascular disease risk reduction, and 1 g/d is recommended for treatment of existing cardiovascular disease. Dietary DHA and EPA mainly come from ocean fish, shellfish, or fish oil supplements. The average intake of seafood in the U.S. is only approximately 3.5 oz per week, while the recommendation is 8-10 oz per week. Therefore, a growing segment of the population elects to take fish oil to increase their intake of DHA and EPA. Dietary fish oil supplements are relatively safe as a whole. In this study, we recruit subjects who consume at least 3 g/wk of DHA and EPA either from seafood, fish oil, or both, for a period of at least 6 months prior to the enrollment. If the subject is taking fish oil per doctor's prescription, we do not want to interfere with the therapy, and will encourage the subject follow the doctor's orders. Clinically, high-dose of fish oil may increase bleeding times, and worsening of glycemic control in diabetics (who will be excluded from the study).

Urine collection: there are no risks with these procedures.

GPS travel recorder: the travel recorder may present some privacy concerns to the subjects regarding the continuous recording of their geographical location. The data obtained using this device are secure and the data is not available in real time for the following reasons: 1) data is stored to internal memory, 2) device has no display and no remote/wireless capability, 3) data will be downloaded to a secure database using a cable connection (i.e., not a wireless connection), 4) data cannot be downloaded without proprietary software (not widely available), and 5) data will be cleared from memory of travel recorder after downloading data.

Hexoskin: the compression shirt may present some privacy concerns to the subjects regarding the continuous recording of their ventilation rate. The data obtained using this device are secure and the data is not available in real time for the following reasons: 1) data is stored to internal memory, 2) device has no display and no remote/wireless capability, 3) data will be downloaded to a secure database using a cable connection (i.e., not a wireless connection), 4) data cannot be downloaded without proprietary software (not widely available), and 5) data will be cleared from memory of recorder after downloading data.

TrackMyAir: There is little risk associated with answering the question presented by the application. All data is de-identified and not stored on the study specific device.

Confidentiality: Risk of breach of confidentiality is minimal. All individuals who have been granted access to the data to perform their research-related duties will be bound by an agreement of confidentiality. All subjects will be assigned a study number which will be used for data recording – not the subject's name. The study number is all that will be entered into computer databases and a numeric coding system will be used to ensure that subjects cannot be directly identified from the samples alone. All information provided by the participant to the investigators and all information that is collected about the participant by the investigators shall be kept confidential to the extent that is provided by law. Computer data files are password protected and coded by an identifying number. The participant's actual identity cannot be ascertained exclusively from these data. Medical charts are secured and maintained in locked files in the EPA HSF medical station and the Facility remains guarded 24 hours a day year round. The participant's name will not be used in any publications. Access to the records of this study will be provided by the identifying number only and given only to those individuals associated with the study who require access to the data to perform their duties. All such individuals will be bound by this agreement of confidentiality.

Some risks may be unforeseeable. The Research Team will keep the Committee and participants informed of any new findings that affect the risk/discomfort involved with this protocol.

A.6.11. Unless already addressed above, describe procedures for referring subjects who are found, during the course of this study, to be in need of medical follow-up or psychological counseling

Study volunteers will be given any new information gained during the course of the study that might affect their willingness to continue participation in the study, and regarding our decision to not allow volunteers to participate in the study (e.g., physical findings, abnormal blood values, heart rhythm irregularities).

It is important to note that all forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, a volunteer may develop an injury or illness due to participating in this study. If a volunteer develops an injury or illness determined by the on duty physician to be due to participation in this research, the EPA will reimburse the volunteer for the medical expenses to treat the injury or illness up to \$5000. If the volunteer believes the injury or illness was due to a lack of reasonable care or other negligent action, the volunteer has the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671et. seq., provides for money damages against the United States when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. By signing the consent form the volunteer does not waive any legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

A.6.12. Are there plans to withdraw or follow subjects (or partners of subjects) who become pregnant while enrolled in this study?

Yes

If yes, explain

All female participants will be tested for pregnancy on the 1st day of each study session. Individuals who become pregnant will be removed from the study.

A.7. Data and safety monitoring

A.7.1. When appropriate, describe the plan for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based data and safety monitoring board or committee (DSMB, DSMC, DMC), depending on the study. For studies that do not raise obvious safety concerns, you may still describe your plans for monitoring the study as it progresses.

The safety of participants will be monitored throughout the course of the study by the investigators and EPA medical staff. Medical staff will check vital signs once the participants arrive at the EPA Human Study Facility to ensure that they are fit to participate in the clinical tests. Additionally, a study physician will be immediately available by pager during all study visits. A fully equipped medical-cart will be accessible at all times with resuscitation medications and equipment. In the event of an emergency during which it becomes necessary to call 911, the UNC Hospitals is in close proximity to our facility.

Additionally, Holter monitor data will be downloaded within 24 hours following the current study visit, and will be assessed by a Registered Nurse or an experienced research personnel prior to the beginning of the next visit. Individuals will be removed from the study if they experience arrhythmias that pose a safety risk, such as symptomatic bradycardia, sustained supraventricular tachycardia, and either sustained (≥ 30 sec or symptomatic for any duration) or unsustained (≥ 3 consecutive ventricular beats) ventricular tachycardia. Any detected abnormality will be brought to the attention of the investigators and the medical staff who will review the information and determine if there is adequate concern to remove the participant from the study. Any abnormality detected will be conveyed to the subject with appropriate advice for follow-up with their primary care physician or sub-specialty physician, when warranted. Any Unanticipated Problem(s) (UP) or Adverse Event(s) (AE), as defined by the UNC IRB, will be reported to the IRB as directed by the published Standard Operating Procedures (19.0). Subjects will be aware of their right to terminate their participation in the study at any time without prejudice or loss of monetary compensation as established in the consent form.

A.7.2. If not already addressed above, describe the plans for aggregate review of unanticipated problems (including but not limited to adverse events) across all sites, in order to monitor subject safety.

After every 5 subjects have completed the study, there will be an interim analysis of trends of unanticipated events, adverse events (if any) and any irregularities related to the study.

A.7.3. What are the criteria that will be used to withdraw an INDIVIDUAL SUBJECT from this study or halt the research intervention (e.g., abnormal lab tests, allergic reactions, failure or inability to comply with study procedures, etc.)?

Individual participants will be withdrawn from the study if they exhibit abnormal lab test values that, in the opinion of the investigators and study physician(s), put them at a reasonable risk for an adverse reaction to any aspect of the study procedure. Individual participants will also be withdrawn from the study if they exhibit signs of physical distress (e.g., chest pain or shortness of breath) during the study visits.

A.7.4. Are there criteria that will be used to stop the ENTIRE STUDY prematurely (e.g., safety, efficacy, unexpected adverse events, inability to recruit sufficient number of subjects, etc.)?

Yes

Please explain

The entire study will be stopped if we are unable to recruit a sufficient number of study participants.

A.7.5. Will this study involve a data and safety monitoring board or committee?

No

A.8. Data analysis

A.8.1. Summarize the statistical analysis strategy for each specific aim.

H0: Cardiovascular response to ambient air pollution is not altered by dietary intake of omega-3 fatty acid fish oil as compared to control.

Ha: Cardiovascular response to ambient air pollution is attenuated by dietary intake of omega-3 fatty acid fish oil as compared to control.

We will associate cardiovascular response endpoints to the interaction of omega-3 fatty acid and ambient PM exposure using multi-level regression analysis. This approach will allow us to account for repeated measures in each of the recruited individuals.

Estimated effect size of the interaction term parameter describes the impact of DHA and EPA supplementation on cardiovascular responses to ambient air pollution, as compared to no supplementation. The magnitude of the interaction of effect size will be determined for daily and lagged exposures to particulate matter and 95% confidence intervals (probability of type I errors, $\alpha = 0.05$) will be estimated from

standard errors generated during the regression fitting procedure. Anticipated power will be 0.80.

While every effort will be made to obtain complete data on subjects according to protocol, we will recruit enough participants to allow for complete loss of data for up to 5 sessions (i.e., one extra person). It is however more reasonable to expect that data loss will be scattered throughout the data set for specific endpoints at various times.

A.8.2. If this is a pilot study, please describe the future study and say how its study design, aims, sample size, and methods differ from the pilot study you are proposing.

This is not a pilot study.

A.8.3. Provide a compelling justification for the proposed sample size in terms of the likelihood of achieving each aim.

Sample size was computed using repeatedly simulated data based on distributions and estimates of effect observed in previous relevant work, conducted by the investigators. Power was determined based on the primary endpoint of LFn measure of heart rate variability. Assuming 5 repeated measures, expected sample size is between 58 and 60. The estimate is based on the assumed increase in LFn after exposure to ambient particulate matter of 12%, and an assumed complete attenuation of the observed increase with omega-3 fatty acid. The assumed degree of attenuation is consistent with the nearly abolished effect observed in a recent chamber study, conducted by the investigators.

This comparable chamber study investigated the impact of fish oil supplementation on the mean LFn change in exposed-CAP participants. Using a sample size of 15, investigators were able to observe the abolishment of increase in LFn in those supplementing with fish oil through ANOVA. In the current study investigating the interaction of omega-3 fatty acid and PM exposure, it is reasonable to expect a 4 fold increase in sample size.

A.8.4. Summarize the plans for data management.

The study investigators will be responsible for ensuring data quality. The study investigators will be assisted by their data management staff in monitoring adherence to protocol. The majority of data inputs are automated from instrumentation into databases, reducing chances of human error in data input.

Federal records will be kept in accordance with document guidelines in NHEERL-H/QA-RK95/00 and ORD's Policy for Paper Laboratory Records. Most Federal records will fall under EPA records schedule 503 "Scientific Research Project Files Related to Basic, Exploratory Research". Non-Federal records (schedule 008), such as technical reference materials and working papers and drafts, will be segregated from Federal records. Federal records will be retained according to the appropriate records schedule.

A.9. Identifiers

A.9.1. Check which of the following identifiers you already have or will be receiving, or select "None of the above."

- ☒ Names (this would include names/signatures on consent forms)
- ☒ Telephone numbers
- ☒ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
- ☒ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes (e.g. GPS coordinates), except for the initial three digits of a zip code
- ☐ Fax numbers

- ☒ Electronic mail addresses
- ☐ Social Security numbers
- ☐ Medical record numbers
- ☐ Health plan beneficiary numbers
- ☐ Account numbers
- ☐ Certificate/license numbers
- ☐ Vehicle identifiers and serial numbers (VIN), including license plate numbers
- ☐ Device identifiers and serial numbers (e.g., implanted medical device)
- ☐ Web universal resource locators (URLs)
- ☐ Internet protocol (IP) address numbers
- ☐ Biometric identifiers, including finger and voice prints
- ☐ Full face photographic images and any comparable images
- ☐ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher
- ☐ None of the above

A.9.2. For any identifiers checked, how will these identifiers be stored in relationship to the research data?

- ☐ with the research data (i.e., in the same data set and/or physical location)
- ☒ separate from the research data (i.e., coded with a linkage file stored in a different physical location)

Provide details about the option you selected above:

All individuals who have been granted data access to perform their research-related duties have received full ethics training and will be bound by an agreement of confidentiality. All information provided by the participant to the investigators and all information that is collected about the participant by the investigators shall be kept confidential to the extent that is provided by law. Computer data files and questionnaires are on a secure password protected server and subjects are coded with an unrelated subject identifying study number. Data will be recorded on paper (charts, data sheets, strip chart recorders) and/or in electronic web-based questionnaire will only be linked using the study number. The participant's actual identity cannot be ascertained exclusively from these data. The participant's name will not be used in any publications. Access to the records of this study will be provided by the identifying study number only and given only to those individuals associated with the study who require access to the data to perform their duties. With signed consent from the participant, the samples will be stored indefinitely for future testing. Portions of the sample may be shared with researchers at other scientific institutions or sent to outside clinical laboratories for analysis, however, only coded samples will be sent. No personal identifiers will leave the Medical Station and all medical charts/records are maintained in a locked room in the medical records office of the 24 hr guarded year round US EPA Human Studies.

A.9.3. Are you collecting Social Security Numbers to be used as a unique identifier for study tracking purposes for national registry or database? (Do not check yes if collecting SSN *only* for payment purposes; this will be addressed later.)

No

A.10. Confidentiality of the data

A.10.1. Describe procedures for maintaining confidentiality of the data you will collect or will receive (e.g., coding, anonymous responses, use of pseudonyms, etc.).

All individuals who have been granted data access to perform their research-related duties have received full ethics training and will be bound by an agreement of confidentiality. All information provided by the participant to the investigators and all information that is collected about the participant by the investigators shall be kept confidential to the extent that is provided by law. Computer data files and questionnaires are on a secure password protected server and subjects are coded with an unrelated subject identifying study number. Data will be recorded on paper (charts, data sheets, strip chart recorders) and/or in electronic web-based diaries will only be linked using this study number. The participant's actual identity cannot be ascertained exclusively from these data. The participant's name will not be used in any publications. Access to the records of this study will be provided by the identifying study number only and given only to those individuals associated with the study who require access to the data to perform their duties. No personal identifiers will leave the Medical Station and all medical charts/records are maintained in a locked room in the medical records office of the 24 hr guarded year round US EPA Human Studies Facility.

The study data will be archived with identifiers by storage in a locked room in the 24hr, guarded year round, US EPA Human Studies Facility building. If offsite storage space is ever required for the data, the data will be transferred to offsite storage according to the US EPA's record keeping guideline.

The GPS data is of great importance to this research project because it will substantially enhance the accuracy of our assessment of the subjects' air pollution exposure. The GPS monitoring does allow the potential for deductive disclosure because the GPS device identifies time and location of subjects during the study period. However, privacy is maintained because the data are not accessible to the subject or subjects' family for the following reasons: 1) The GPS unit does not have a direct display and cannot be visualized by the subject or the subjects' family or other contacts. 2) The device has no remote/wireless connection and the data will be directly downloaded at the medical station onto a secure EPA server which is password protected. 3) The data can only be visualized using proprietary software purchased from the manufacturer. 4) The data will be downloaded to a secure database using a cable connection (i.e., not a wireless connection). 5) This GPS data will not be stored in combination with any other identifiers that might facilitate deductive disclosure of subject identification. (6) The data will be cleared from memory of travel recorder after downloading data.

A.10.2. Describe how data will be transmitted among research team (i.e., personnel listed on this application).

In general, information will be transmitted between the study investigators with paper, verbal, and encrypted electronic transmissions. The information will include pertinent medical history, physical examination, lab studies, and information relating to study endpoints (e.g. spirometry, and cardiac physiology data). Within the EPA building, there will be communication between the FEFA Recruitment Office and the study investigators with regards to participant qualification.

A.10.3. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc?

No

A.10.4. Do you plan to obtain a federal Certificate of Confidentiality for this study? Please note that all ongoing or new research funded by NIH as of December 13, 2016 that is collecting or using identifiable information is [automatically issued a Certificate of Confidentiality](#) (CoC). You should also select "Yes" if your study is NIH funded and has been issued a CoC under this updated NIH policy.

No

A.10.5. If this study is limited to data collection by survey or interview, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

The potential for deductive disclosure is not likely in this study since the variables collected could not reasonably be used in aggregate to identify a single individual in this population.

A.10.6. Will any of the groupings or subgroupings used in analysis be small enough to allow individuals to be identified?

No

A.11. Data sharing and transmission

A.11.1. Check all of the following who will receive **identifiable data** (contains any of the 18 identifiers listed above) outside the immediate research team (i.e., not listed as personnel on this application)? *

- ☒ No one
- ☐ Coordinating Center
- ☐ Statisticians
- ☐ Consultants
- ☐ Other researchers
- ☐ Registries
- ☐ Sponsor and/or its designee(s)
- ☐ External labs for additional testing
- ☐ Journals
- ☐ Publicly available dataset
- ☐ Other

A.11.2. For any recipients checked above, explain the confidentiality measures to be taken

No Answer Provided

A.12. Post-study disposition of identifiable data or human biological materials

A.12.1. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. If you plan to destroy linkage codes or identifiers, describe how and when this will be done.

The study data will be archived with identifiers by storage in a locked room in the secured US EPA HSF building. If offsite storage space is ever required for the data, the data will be transferred to offsite storage according to the USEPA's record keeping guidelines. All specimens remaining after the completion of the study will be stored with only an alphanumeric specimen number identifier in a secured freezer in accordance with the EPA Human Studies Facility protocol, titled "Repository for storage of human specimens" (IRB approved protocol #07-1768). Identifying information in records that could be used to link participants to specimen numbers will be protected by an "honest broker" system in which only EPA medical station nurses will be able to link specimen numbers to the associated personal identifying information. The honest broker system is described in Appendix O of the UNC-CH Human Research Protection Program's standard operating procedures. Only the Principal Investigator, Co-investigator and laboratory technical staff identified on the protocol will have access to the repository. The Co-investigator will assume contingency responsibility for security of participant files, specimens, and future studies in the absence of the Principal Investigator. Specimens and data deriving from this study may be released to other investigators for more comprehensive studies with appropriate US EPA approval. In the event of their release to other investigators the specimens and/or data will carry only the alphanumeric code originally assigned and will be identifiable only to the Principal and Co-investigator. Specimens from subjects who opt not to allow for storage will be destroyed at the end of the study. Subjects at any time may request, in writing, that their samples no longer be stored in the repository. Any analysis in progress at the time of the request or already performed prior to the request being received by the researcher will continue to be used as part of the research study. Once the researcher has obtained written notification, the requesting subject's specimens will be destroyed.

Part B. Direct Interaction

B.1. Methods of recruiting

B.1.1. Check all the following means/methods of subject recruitment to be used:*

- ☐ In person
- ☐ Join the Conquest
- ☐ MyChart

Use of MyChart for research recruitment purposes is currently available only to studies which meet specific criteria to participate in a pilot test. Please contact [Stephanie Deen](#) if you would like to see if your study meets the criteria for this use.

☒ Participant pools

☒ Presentation to classes or other groups

☒ Letters

☒ Flyers

☒ Radio, TV recruitment ads

☒ Newspaper recruitment ads

☒ Website recruitment ads

☒ Telephone script

☒ Email or listserv announcements

☒ Follow up to initial contact (e.g., email, script, letter)

☒ Other

B.1.2. Describe how subjects will be identified

Volunteers will be recruited for this study by FEFA Corporation under contract with the U.S. EPA. The manner in which this will be done is similar to past U.S. EPA studies and specific recruitment procedures as per the previously UNC IRB-approved protocol, Recruitment and Screening of Potential Participants for EPA Studies (IRB #95-0518).

Potential volunteers will self-identify in response to the advertising described in section B.1.1. The exception will be for those identified from a pool of previous volunteers who are selected based on study eligibility criteria. Omega index results from IRB Study 15-2960 will be obtained to identify participants and used as eligibility criteria if the subject consents to use of this value. Any previous volunteers that meet the study criteria will be contacted via an IRB approved email or phone script. After they are provided information about the study, they will elect whether or not to respond.

B.1.3. Select any of the following procedures solely conducted for screening, recruiting, or determining the eligibility of prospective human subjects. (Note: you should only collect the minimal information needed for these purposes.)

☒ Obtain information through oral or written communication with the prospective subject or legally authorized representative

This includes online, telephone, or in-person screening questionnaires or interviews.

☒ Obtain already collected identifiable private information or records

Examples include review of medical charts, data repositories, and administrative records.

☒ Reviewing/testing identifiable biospecimens by accessing stored biospecimens and related information

☒ None of the above

B.1.4. For any selections made, please describe the procedures. (Respond "N/A" if "None of the above" is selected.)

N/A

B.1.5. For any information collected for these purposes, please describe when and how you will destroy the data if the participant declines to participate or is not eligible. (Respond "N/A" if "None of the above" is selected.)

N/A

B.1.6. Describe how and where subjects will be recruited and address the likelihood that you will have access to the projected number of subjects identified in A.2.

Subjects will be recruited for this study by FEFA Inc, which has recruited for studies at the U.S EPA HSF for several years. The manner in which this will be done is similar that that of past U.S. EPA studies and specific recruitment procedures as per previously UNC IRB-approved protocols, Recruitment and Screening of Potential Participants for U.S. EPA Studies (95-EPA-66). Every effort will be made to recruit women and members of racial minority groups into this study. Subjects will be asked to call the recruitment office. During an initial telephone interview, the subjects will receive information regarding the study and their eligibility status will be assessed by answering how long and how often they have been taking fish oil and fish/shellfish (see Form PCS-0). Subjects whose responses indicate that they are likely to meet the criteria (for example, taking at least 5 pills of fish oil per week for the past 6 month or longer, or have not taken fish oil pills and consumed no more than 1 serving (4-6 oz) of fish or seafood per month at least for the past 6 months) will be scheduled for an omega-3 index screening. Subjects whose responses indicate that they do not meet the above criteria but have been consistently taking a combination of fish oil supplements (less than 5 pills of fish oil per week for more than 6 months) and high level of ocean fish/shellfish intake will be assessed for eligibility by a Registered Dietitian via phone prior to admission for the screening. During the screening visit, omega-3 fat intake assessment (Form PCS 6) and a finger prick will be performed. Subjects with blood omega-3 index of 6.5% or higher, or approximately 4% or lower will be scheduled for the physical exam. If the subjects' omega-3 index fall between approximately 5.5% (5.5% included) to 6.5%, their eligibility will be further determined based on their omega-3 fat intake assessment: the ones with at least 3 g/wk of dietary consumption of EPA and DHA will be considered for the study.

B.1.7. Describe how you will protect the privacy of potential subjects during recruitment

Emails will be sent from password protected computers with email stored on secure servers. Email subject lines will state either "Study at the US EPA" or "Your appointment at the EPA Human Studies Facility". All phone calls and phone screening interviews will be conducted from private offices in the EPA Human Studies Facility. On site screening will also be conducted in private offices so that no personal information is shared with other research volunteers. More than one volunteer may be present in the waiting room at one time, but personal information will not be discussed in that area.

B.1.8. Describe how subjects will be contacted, if not addressed above

Potential volunteers will contact FEFA by phone, or by email from the recruitment web site (www.epastudies.org). FEFA will respond either by phone or by email.

B.1.9. Describe who (by role) will do the recruiting

FEFA, Inc. will provide recruitment services to support this study. FEFA is a Contract Research Organization under contract with the US EPA to provide support services for human research at the Human Studies Facility in Chapel Hill, NC. FEFA staff members are CITI and COI trained and certified.

B.1.10. Describe efforts to ensure equal access to participation among women and minorities

Every effort will be made to include women and minorities in this research. Advertising will be placed in a variety of locations to allow widespread access to recruitment information.

B.2. Protected Health Information (PHI)

Protected Health Information (PHI) is any identifiable information about the subject's health that relates to their participation in this research and is obtained from sources other than the subject, such as medical records, health care providers, insurance plans, etc. [more](#)

B.2.1. Are you requesting a limited waiver of HIPAA authorization?

If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a [limited waiver of HIPAA authorization \(see SOP 1801. 2.3\)](#). This does not apply to situations where you will never contact subjects directly (e.g., retrospective chart review), in which case you should request a full waiver under section D.

No

- B.2.2. Will you need ongoing access to PHI (e.g., medical records) to conduct the study, beyond the identification of potential subjects as addressed above? In this case you will need to obtain a signed HIPAA Authorization from each subject.

No

B.3. Subject Contact, Duration and Privacy

- B.3.1. Number of contacts per subject (contacts includes in-person, telephone, email, mailings, etc.)

Varies, depending on how many study sessions the subject participate in. Each subject will have at least 1 visit for omega-3 screening, and 1 visit for physical examination prior to the study. In the study protocol, each study session includes 2 day visits. Study consent will be obtained on the first day visit of study session 1. We anticipate approximately 12 contacts per subject based on participation of the full 5 study sessions protocol. Phone calls might be used to answer or clarify dietary criteria.

- B.3.2. Duration of each contact. If multiple contacts, provide the range or average time for each contact.

Individual visits will vary between 2 to 4 hours.

- B.3.3. Total duration of individual subject's participation, including follow up evaluation, if applicable

Total duration will be based upon subjects' availability for the study sessions. Subjects who are determined to be eligible to participate in the study will be scheduled for up to 5 two-day visits sessions. They will be scheduled with at least one week apart.

- B.3.4. Where are you studying subjects or obtaining their data?

Non-healthcare setting

- B.3.5. Provide more information about the location(s) where research will be conducted (e.g., if UNC Medical Center is checked in #4 above and study visits will be conducted in the CTRC, enter "CTRC" here.)

Participants will be studied at the United States Environmental Protection Agency Human Studies Facility located at 104 Mason Farm Road, Chapel Hill, NC 27514.

- B.3.6. Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope)

All interviews and phone conversations will be conducted in private rooms in the U.S. EPA Human Studies Facility, a secure Federal Facility with 24 hour security guard service year round, people entering the facility must present a government issued photographic identification, and only individuals working in the building have access beyond the guard's desk without an escort. Physical exams and other procedures will occur in appropriate clinical areas of the EPA. Occasionally, other subjects may be seen in the clinical area at one time; however, sensitive information is only discussed in private (medication use, pregnancy test results). Subjects may be contacted by email to schedule/remind them about study visits or to answer specific questions. Any information sent via US mail or campus mail will simply have a return address, no other study specific information.

B.4. Incentives for participation

- B.4.1. Are there incentives (monetary or non-monetary) for subjects to participate or are you reimbursing subjects for study-related costs (e.g., travel, parking, hotel accommodations or childcare)?

Yes

- A. Please describe any incentives and/or reimbursements for study-related costs separately below.

Money received by participants in research studies is normally treated as ordinary income by taxing authorities and payments made to participants will be reported to the Internal Revenue Service as required by law. FEFA Corporation will collect participants' social security numbers for income reporting purposes as indicated in IRB #95-0518. The money is not intended to coerce completion or participation, but to emphasize the importance of all the visits, and to signify the importance of participants' time and commitment to the

research study.

Subjects will receive monetary compensation for their time (approximately \$12 per hour) and for procedures in the study. In addition, subjects traveling from areas beyond Chapel Hill/Carrboro will be reimbursed for travel expenses commensurate with the US Government mileage rate in effect at the time. Parking will be provided or costs will be paid. The following table details the expected compensation for completion of the entire study:

Omega-3 screening (a separate consent) \$20

Study session 1

1st day visit (approximately 4 hours) \$50

- Vital signs check
- Informed consent (Form PCS-1 to Form PCS-5)
- Urine test
- A Residence and Participant Survey (Form PCS-9)
- A baseline dietary food frequency questionnaire (online access) instruction (Form PCS-12) and dietary counseling on portion size (Form PCS-8)
- A list of Low Fat Breakfast and Lunch Choices (Form FCS-11)
- Spirometry training
- Holter placement
- GPS recorder and activity monitor placement

2nd day visit (approximately 3 hours) \$150

- Vital signs check
- Blood draw
- HRV
- BAU
- Retinal image
- Spirometry
- A Daily Follow-up Questionnaire (Form PCS-10)

Study session 2-5

1st day visit (approximately 2 hours) \$50

- Vital signs check
- Urine test
- Dietary 24 h recall (Form PCS-7)
- Holter placement
- GPS monitor and activity monitor placement

2nd day visit (approximately 3 hours) \$150

- Vital signs check

- Blood draw
- HRV
- BAU
- Retinal image
- Spirometry
- A Daily Follow-up Questionnaire (Form PCS-10)

Study completion**\$125**

- Food frequency questionnaire
- Study completion bonus

Maximum payment = \$1145

B. Specify the schedule for incentives and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it.

A subject who is unable to complete the study for voluntary reasons or failure to comply with eligibility requirements will receive full compensation for his/her participation up to the point of their departure from the study. In the event a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, the subject will be paid at the standard hourly rate for the time scheduled and canceled. Cancellations could occur due to adverse weather conditions, equipment failure, or other unforeseen events. When feasible, the subject will be rescheduled.

C. For compensation in foreign currency, provide a US dollar equivalent.

All payments are in US currency.

D. Discuss the potential for coercion, given factors like the amount of the incentive, the age of the subjects, the purchasing power in foreign countries, the time involved and complexity of procedures, etc.

The compensation is not intended to coerce completion or participation, but to emphasize the importance of all the visits, and to signify the importance of the subject's time and commitment to the research study. Based on hourly rates of compensation that were approved in other studies with similar protocols and/or levels of risk, the above-detailed pay schedule was felt to be commensurate with other existing studies' pay structure.

E. If the subjects are children who will receive the compensation, i.e., the child, the parents or both?

Participants will be between the ages of 25 and 55 years.

B.4.2. Are you collecting Social Security numbers or ITIN for payment and/or tax-related purposes?

No

B.5. Costs to be borne by subjects

B.5.1. Will there be any costs that subjects will incur related to participation in the study? Do not include costs for standard care for which patients would be billed if they were not in this study. Also do not include the time spent participating in the study.

No

Part C. Existing Data, Records, Specimens

C.1. Data Sources

C.1.1. What existing records, data or human biological specimens will you be using? (Indicate all that apply or select 'None of the above'):

☒ Medical records in any format.

ALERT: You must check both boxes: 1) Medical records in any format and 2) Electronic medical record using Epic, or you/your study team will not be granted access to Epic for research purposes.

☒ Electronic medical records using Epic, WebCIS or other electronic system

☒ Carolina Data Warehouse for Health (CDW-H) (for UNC and its affiliates only)

☒ Carolinas Collaborative Data Request and Review Committee (DRRC)

☒ Paper medical records

If you access the medical records of fewer than 50 patients under a full or limited waiver of HIPAA, submit a copy of your IRB approval letter and a completed [Research Disclosure Form](#) to Health Information Management (HIM). Do not submit this information to the IRB. For additional information about this process, you should contact HIM directly at : 919-595-5591 or 919-966-1225 or 919-595-5580.

☒ Data already collected from another research study

Were the investigators for the current application involved in the original collection? --

☒ Patient specimens (tissues, blood, serum, surgical discards, etc.)

Has the clinical purpose for which they were collected been met before removal of any excess? --

☒ Data already collected for administrative purposes

☒ Student records ([You will need to satisfy FERPA requirements: see SOP 3101, section 3.1 for guidance](#))

☒ UNC Dental Records

☒ Data coming directly from a [health plan, health care clearinghouse, or health care provider](#)?

☒ Publicly available data

☒ Other

☒ None of the above

For EACH data source checked above, provide a description of the data, proposed use, how data were collected (including consent procedures), and where data currently reside.

--

C.1.2. Describe your plans for obtaining permission from the custodians of the data, records or specimens (e.g., pathology dept, tissue bank, original researcher):

Does not apply.

C.1.3. Do the custodians of the data, records or specimens require a data use agreement?

No

C.2. Coding and Data Use Agreements

C.2.1. When you receive these data, records or human biological specimens will they be coded? Coded means identifying information that would enable the research team to readily ascertain the individual's identity has been replaced with a number, letter, symbol, or combination thereof (i.e., a code). If you will not be using existing materials, check "No."

No

Part D. The Consent Process

D.1. Obtaining informed consent from subjects

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances. If you will be requesting a waiver answer "not applicable" for any of the following questions that will not pertain to this study. You will be asked to provide relevant information in the section below on waivers.

D.1.1. Will children under the age of majority in their locale (18 years in NC) be enrolled?

(Note: Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.)

No

D.1.2. Will adult subjects be enrolled in your study?

Yes

Explain the process for obtaining consent from the subject.

The participants will be required to read and sign a consent form asserting that they have read and understood the following:

1. Participation is strictly voluntary
2. The purpose of the study including the societal benefits
3. The nature and extent of participation
4. Rights to withdraw from the study at any time
5. Right to privacy
6. The risks associated with participation
7. The method and schedule of compensation
8. The limits of liability with respect to the EPA and the PI.

The PI, Co-Investigator or study coordinator will then review the contents of the consent form and go through a check list highlighting important points from the consent form and answer any questions that the volunteer may have before the volunteer signs it. Subjects will have the opportunity to ask questions at any time during the study by contacting the PI, Co-Investigator, study coordinator or Medical Station. The subject will be given a copy of the signed consent form for his/her records.

D.1.3. Will decisionally-impaired subjects be enrolled in your study? (includes unconscious patients, some psychiatric disorders, others who lack the capacity to give consent)

No

D.1.4. Are you planning to obtain consent from any Non-English speaking subjects?

No

D.1.5. Describe who (by role) will be obtaining consent or parental permission.

One of the individuals listed on the front page of the application in the role of study Principal Investigator, Co-investigator, or Study Coordinator will be responsible for obtaining informed consent from the study volunteers.

D.1.6. Discuss the potential for influencing the subject's decision to participate. Describe steps that will be taken to minimize undue influence during the consent process. These might include a waiting period between the initial consent discussion and obtaining consent, or obtaining consent by someone other than a person with perceived authority (e.g., professor, employer, treating physician).

Informed consent will not be obtained during the initial phone/letter contact. This will occur at their first study visit prior to enrollment into the study. Informed consent will be obtained by the Principal Investigator, a study Co-investigator, or Study Coordinator. The potential subject will be informed that they can take as much time as needed to read the consent form and that they should not sign until all their questions have been addressed.

D.1.7. Has the sponsor of this study provided a model consent form?

No

D.2. Waiver of written documentation of informed consent

The default is for subjects to sign a written document that contains all the elements of informed consent. Under limited circumstances, the requirement for a signed consent form may be waived by the IRB. For example, this might occur for phone or internet surveys, when a signed consent form is either impractical or unnecessary, or in circumstances where a signed consent form creates a risk for the subject.

D.2.1. Are you requesting a waiver of any aspect of written (signed) documentation?

No

D.3. Full or partial waiver of consent

The default is for subjects to give informed consent. A waiver might be requested for research involving only existing data or human biological specimens. More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

D.3.1. Are you requesting any of the following:

- ☒ a waiver of informed consent in its entirety
- ☒ a waiver or alteration of some of the elements of informed consent
- ☒ a waiver of HIPAA authorization (If you are accessing patient records for this research, you must also request a waiver of HIPAA authorization)

D.3.2. If your request for a waiver applies to some but not all of your subject groups and/or consent forms, please describe and justify

No Answer Provided

D.3.3. Does this request for waiver support a study design that involves deception or withholding of information?

No

Consent Forms

This submission requires the following consent forms

Template Type

Adult Consent Form

Stored Specimens with Identifiers

This submission includes the following consent forms

File Name	Document Type
PISCES-Omega-3_Screening_Modification_4-12-18.doc	Adult Consent Form
PISCES_Main_Consent_Revision_5-14-19_1.docx	Adult Consent Form
OMEGAScreening_Consent_Addendum_for_Current_Subjects_09252017.docx	Consent Addendum for Current Subjects
OMEGA_Index_Addendum_for_Current_Subjects_05032018 (1).docx	Consent Addendum for Current Subjects
PISCES-ConsentChecklist_Revision_11-15-2018 (5).docx	Other Consent Materials
PISCES-Genotyping_Revision_11-15-18 (4).doc	Other Consent Materials

PISCES-RecontactConsentForm_Revision_11-15-18 (4).docx

Other Consent Materials

PISCES-StorageConsent_Revision_11-15-18 (4).docx

Stored Specimens with Identifiers

[view consent forms](#)**Attachments****This submission requires the following attachments****Document Type**

Pencil and Paper Questionnaire Survey

Electronic Questionnaire Survey

Device Description

Letter for Recruitment

Flyer for Recruitment

Newspaper Ad for Recruitment

Website for Recruitment

Telephone Script for Recruitment

Email or Listserv Recruitment

Recruitment Follow Up

This submission includes the following attachments

File Name	Document Type
About Us - Hexoskin _ Carre Technologies inc (Hexoskin).pdf	Device Description
Hexoskin Smart Shirts - Cardiac, Respiratory, Sleep & Activity Metrics.pdf	Device Description
IRB 16-1048 Investigational-Device-Worksheet-ver.10-05-2016.pdf	Investigational Device Worksheet
PISCES Email Announcement 3-21-17.pdf	Email or Listserv Recruitment
PISCES Email Announcement Omega3 3-21-17.pdf	Email or Listserv Recruitment
PISCES UNC List Server Email Announcement 3-21-17.pdf	Email or Listserv Recruitment
PISCES UNC List Server Email Announcement OMEGA3 3-21-17.pdf	Email or Listserv Recruitment
Pisces Appoitnment Email Reminder 7-6-17.pdf	Recruitment Follow Up
Pisces Omega-3 index screening Appointment Email Reminder 7-10-17.pdf	Recruitment Follow Up
PISCES Omega-3 Flyer 3-21-17.pdf	Flyer for Recruitment
Pisces Flyer 3-21-17.pdf	Flyer for Recruitment
Pisces recruitment script 3-21-17.pdf	Letter for Recruitment
Pisces newspaper-craigslist ad 3-21-17.pdf	Newspaper Ad for Recruitment
Pisces newspaper-craigslist ad Omega3 3-21-17.pdf	Newspaper Ad for Recruitment
PISCES Web based search ad 3-21-17.pdf	Other Materials for Recruitment
PISCES questionnaire 10-26-16.pdf	Telephone Script for Recruitment
PISCES Web Site 3-21-17.pdf	Website for Recruitment
PortionSize 4-3-16.pdf	Diaries Journal Guide
DHQ 4-3-16.pdf	Electronic Questionnaire Survey
PCS-12_DHQ_Instructions_for_Participants_11262018 (1).docx	Interview Questionnaire Survey
24 Hour Dietary Recall 4-3-16.docx	Pencil and Paper Questionnaire Survey
Preliminary nutrition screening 3-30-17.docx	Pencil and Paper Questionnaire Survey
daily_follow_up_questionnaire.pdf	Pencil and Paper Questionnaire Survey

residence_and_participant_survey.pdf	Pencil and Paper Questionnaire Survey
Hexoskin_irb_pisces.docx	Other
PISCES payment voucher.pdf	Other
PISCES-LowFatBreakfast 2-9-17.doc	Other
Phone Script 4-3-16.docx	Other
TracMyAir_irb_pisces (002).docx	Other
MattCitiTraining.pdf	Research Ethics Training

[view attachments](#)

Addenda

 Data Security Requirements

[view addenda](#)

If Principal Investigator of this study is a Student or Trainee Investigator, the Faculty Advisor certifies the following:

I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

By certifying below, the Principal Investigator affirms the following:

I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

This study proposes research that has been determined to include Security Level 2 data security requirements. I agree to accept responsibility for managing these risks appropriately in consultation with departmental and/or campus security personnel. The Data Security Requirements addendum can be reviewed [here](#).

Certifying Signatures:**Signature:** Electronic Signature Received**Date:** 4/17/2019 04:05:47 PM

Haiyan Tong

University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Addendum to provide additional information to subject after original consent

Consent Form Version Date: 05/03/2018

IRB Study # 16-1048

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong

Principal Investigator Department: Aux Services Affiliates: EPA

Principal Investigator Phone number: (919) 966-4993

Principal Investigator Email Address: tong.haiyan@epa.gov

Funding Source and/or Sponsor: United States Environmental Protection Agency (EPA)

Study Contact Telephone Number: (919) 966-6234

Study Contact Email: salazar.claudia@epa.gov

The following information should be read as an addition to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated otherwise in the following paragraphs, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may choose not to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

This consent form requests your permission to access your Omega-3 Index value obtained in IRB Study #15-2960, Title: "Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects" to use for confirmation of eligibility in this current study. This would eliminate the need to collect this sample from you again. This request does not increase your risk in participating in this study.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to continue to participate in this research study.

Signature of Research Participant

Date

Printed Name of Research Participant

Signature of Research Team Member Obtaining Consent

Date

Printed Name of Research Team Member Obtaining Consent

University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Addendum to provide additional information to subject after original consent

Consent Form Version Date: 09/25/2018

IRB Study # 16-1048

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong

Principal Investigator Department: Aux Services Affiliates: EPA

Principal Investigator Phone number: (919) 966-4993

Principal Investigator Email Address: tong.haiyan@epa.gov

Funding Source and/or Sponsor: United States Environmental Protection Agency (EPA)

Study Contact Telephone Number: (919) 966-6211; (919) 966-6234

Study Contact Email: case.martin@epa.gov; salazar.claudia@epa.gov

The following information should be read as an addition to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated otherwise in the following paragraphs, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may choose not to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

This consent form requests your permission to re-draw your Omega-3 Index screening sample. Your previous collected sample was mailed, but not received by the laboratory. This sample was de-identified and did not include any of your personal identifying information. This unexpected event did not breach your confidentiality and does not increase your risk in participating in this study.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to continue to participate in this research study.

Signature of Research Participant

Date

Printed Name of Research Participant

Signature of Research Team Member Obtaining Consent

Date

Printed Name of Research Team Member Obtaining Consent

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects
Biomedical Form

IRB Study # 16-1048

Consent Form Version Date: 5.14.2019

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Co-Principal Investigators: James Samet, PhD, MPH; Hao Chen, PhD

UNC-Chapel Hill Department: US Environmental Protection Agency

Principal Investigator Email Address: tong.haiyan@epa.gov

Funding Source: US Environmental Protection Agency Intramural Federal Research

Study Contact telephone number: (919) 966-4993, (919) 966-0665, (919) 966-9427

Study Contact email: tong.haiyan@epa.gov; samet.james@epa.gov; chen.hao@epa.gov

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary.

You may refuse to join, or you may withdraw your consent to be in the study, for any reason at any time.

Research studies are designed to obtain new knowledge that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Your participation is voluntary. Deciding not to be in the study or leaving the study before it is complete will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The main purpose of this research study is to determine if dietary consumption of EPA and DHA, two important omega-3 fatty acids, affects cardiopulmonary responses to ambient air pollution in healthy adults. Results from this study will expand our knowledges in utilizing dietary strategies to combat the adverse effects of exposure to air pollution.

You are being asked to be in this study because:

Initial/Date _____

- You are 25-55 years old, generally healthy.
- You have a normal resting electrocardiogram (ECG) and lung function, and have no history of heart arrhythmia.
- Your oxygen saturation is greater than 96% at the time of physical exam.
- You have been taking a relatively high amounts of EPA and DHA from dietary supplements and/or foods (cumulatively taking EPA and DHA greater than 3 grams per week) at least 6 months prior to your enrollment, and your blood omega-3 index is approximately 5.5% or higher; OR you have been taking no more than 1 pill/month of fish oil supplement, or more than 1 serving size (4-6 oz)/month of ocean fish/shellfish during the 6-month period preceding enrollment, and your blood omega-3 index is approximately 4% or lower.

Are there any reasons you should not be in this study?

You should not participate in this study if...

- You have a history of acute or chronic cardiovascular disease, such as myocardial infarction.
- You have a history of chronic respiratory disease, such as COPD, or you have been diagnosed by your physician with persist moderate to severe asthma.
- You have a history of active cancer (possible exception for history of non-melanoma skin cancer).
- You have uncontrolled high blood pressure (≥ 150 systolic, ≥ 90 diastolic).
- You are a diabetic (previously diagnosed or with hemoglobin A1c level $>6.4\%$).
- You have a body mass index (BMI) >35 or <19 . Body mass index is calculated by dividing your weight in kilograms by the square of your height in meters.
- You are currently smoking or have a smoking history within 1 year of the study (defined as more than one pack of cigarettes in the past year) or have a greater than/equal to a 5 pack year smoking history. This includes tobacco smoking, vaping, or using hookah or e-cigarettes.
- You are living with a smoker who smokes inside the house.
- You are regularly exposed to high levels of vapors, dust, gases, or fumes.
- You are currently taking β -blocker medications (such as atenolol, metoprolol, propranolol, and acebutolol).
- You are currently taking statins.
- You are pregnant or attempting to become pregnant.
- You are unwilling or unable to maintain your current dietary and medication pattern for the whole study.
- You have history of skin allergy to tape or electrodes.
- You have active allergies.
- You have bleeding or clotting disorders.
- You have unspecified illnesses, which in the judgement of the investigators might increase the risk associated with the clinical procedures.
- You had recent (within 6 months) abdominal and/or eye surgery, or been diagnosed with any type of hernia, as well as any other contraindications for raised intra-abdominal pressure.
- You have had an acute respiratory illness within the last 2 weeks.

Initial/Date _____

You should **NOT** participate if you are unable to comply with the following requirements:

- Avoid alcohol, strenuous exercise, and exposure to a high level of vapors, dust, gases or fumes for 24 hours before and during all visits.
- Do not consume coffee/caffeinated beverages 12 hours before all visits.
- Do not eat pan-fried, greasy, or high fat content food 12 hours prior to the 2nd visit day for each study session.

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately 60 people in this research study.

How long will your participation in this study last?

You will have up to 5 sessions (each session includes 2 consecutive days) to the EPA Human Studies Facility if you are eligible for the study (see attached study design flow diagram). Your sessions will be scheduled with at least one week interval between sessions.

What will happen if you take part in the study?

Before you agree to participate in this study, you must read the consent form in its entirety. The research and medical staff will then answer all of your questions and explain all of the risks involved in this study to your satisfaction.

You should have already undergone an omega-3 index screening and a general physical examination to ensure that you are a candidate for this study. If you are a female participating in this study, you should have been asked about your menstrual history.

You are required to avoid 1) alcohol and exposures to a high level of vapors, dust, gases or fumes for 24 hours before all visit days, and 2) coffee and caffeinated beverages 12 hours before all visits. You also are required **NOT** to eat greasy or high fat content food for 12 hours prior to the 2nd visit day for all study sessions. A list of Low Fat Breakfast (Form PCS-11) will be provided to you.

Today is your 1st visit day of the 1st study session which will last approximately 4 hours. The rest of the 1st visits should last approximately 2 hours. First, you will read the consent forms (Form PCS-1 to PCS-5) and have the study described to you. You will be given the opportunity to have any questions answered before signing the consent forms. You will sign two consent forms of each type, one for you to take home and one for our records. Your enrollment is conditional on the signed consent forms. Then, you will complete a Residence and Participant Survey and the TracMyAir smartphone application administered by study personnel to estimate pollutant exposures in your home (Form PCS-9). You will also be asked to complete a baseline dietary food frequency questionnaire which is an online version (you will be given the instruction Form PCS-12). The questionnaire needs to be completed before your second study session. Our dietitian or an experienced study personnel will help you with the estimation of portion size (Form PCS-8) to complete the questionnaire. There may be a training for spirometry (lung function test) for you today. You will breathe through a filter into a clinical machine. We

Initial/Date _____

will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. You do not have to repeat this procedure if you had the spirometry done well from previous studies or from physical exam. We will ask you to do this several times. This test measures the volume of air that can be exhaled and the rate of airflow during exhalation after a maximal inhalation. We will measure your chest and torso using a tape measure to fit you for a Hexoskin shirt. For men, the circumference of the thorax just below the pectoral muscles, and the circumference at the navel line will be measured after a full exhalation. For women, the circumference of the thorax just below the breasts, and the circumference at the navel line will be measured after a full exhalation. The breathing sensors on the Hexoskin shirts will measure continuous displacement of the chest bands for each inhalation to determine minute ventilation (volume of air inhaled per minute). The breathing sensors in the Hexoskin shirt will be calibrated using the pneumotach to true measure the minute ventilation while you perform different physical activities for 3-min durations (e.g. sitting and walking on treadmill at 3 mph, 2% elevation). The data will be downloaded from the recording device via a USB cable connection and stored the data on a secure EPA desktop computer, and the data from the recording device will be erased.

The following activities will occur on the first and/or the following study sessions:

1st visit day:

1. **Vital signs checks:** your vital signs will be checked upon arrival at each visit.
2. **Urine test:** if you are a female, your urine sample will be collected to check for pregnancy.
3. **Heart rate variability (HRV) measurements:** We will record your heart rate using a small portable device called Holter Monitor (a small recording device about the size and weight of a portable tape player). It may be necessary to clean and shave the areas of your chest where the ECG leads will be placed. Excessive deodorant, skin lotions, and body sprays may interfere with the function of some of these leads so we will ask you not to apply these to your chest area on the days you report to the Human Studies Facility. The leads will be connected to a Holter monitor to obtain readings of your heart rate and rhythm. At the end of the day, the Holter monitor will be removed, and the electrodes will be remained for the next day measurement. The data will be analyzed after the study is finished. This device will allow us to detect small changes in how your nervous system regulates your heart beats.
4. **TracMyAir:** The TracMyAir App will be used by study personnel each day you visit the EPA health study facility. The App will not be installed on your phone. The study staff will ask you questions on your home building characteristics, home operating conditions, time-spent in different outdoor and indoor environments, and time-spent at different physical activity levels to calculate your exposure to air pollution. The study personnel will input data for you into the App on an EPA provided smartphone. TracMyAir does not save the calculated exposures on the smartphone and the data is de-identified.
5. **24 h dietary recall** (Form PCS-7): will be administrated on your 2nd session and the subsequent study sessions to assess your compliance with dietary routine. This is a

Initial/Date _____

quantitative research method used in nutritional assessment, which asks you to recall all foods and beverages you consumed during the previous day.

6. **GPS travel recorder:** will be issued to you today and the 1st visit day of all subsequent study sessions, and returned to facility on the next day. This device continuously monitors GPS coordinates and records internally. You will carry the device at all times (24 hours) to record your location so that we can assess your exposure to air pollution during the day. The location data are not displayed and are only available to download with proper proprietary software after your session. Data will be downloaded and stored onto a secure database.
7. **Activity monitor:** will be issued to you today and the 1st visit day of all subsequent study sessions, and returned to facility on the next day. You will wear the device at all times (24 hours) to record the level of your physical exertion. This measurement can be useful in estimating exposure over a given time period.
8. **Hexoskin:** will be issued to you today and the 1st visit day of all subsequent study sessions, and returned to facility on the next day. You will wear the device at all times (24 hours) to record your daily inhaled dose of ambient air pollution. The Hexoskin breathing sensors will be calibrated today while you are wearing the shirt. You will be asked to breathe through a filter into a clinical machine and complete two 3-minute activities: 1.) while you are sitting comfortably and 2.) walking on the treadmill at 3mph at a 2% incline. You will be asked not to bathe or shower during the recording period. Data will be downloaded and stored onto a secure database and data on the recorder will be erased once it has been downloaded.

2nd visit day:

Your vital sign will be checked upon arrival. The GPS travel recorder, activity monitor and a Daily Follow-up Questionnaire (Form PCS-10) will be collected from you to estimate your exposure to air pollution over the past 24 hour. The following clinical measurements will be conducted:

1. **HRV measurements:** You will be asked to recline quietly and breathe at a constant rate for 20 minutes in subdued light, after which the ECG monitor will take a 10-minute measurement of your heart rhythm. It is important that you do not fall asleep during this 30-minute period.
2. **Brachial artery ultrasound (BAU):** After the HRV measurement, the diameter of an artery in your upper arm will be measured by an ultrasound machine. The ultrasound operator will scan your arm with a probe and then place a tourniquet on your arm, much like a cuff used to measure blood pressure. The cuff on your arm will be inflated for 5 minutes in order to stop the flow of blood. You may feel sensations similar to that when your foot “goes to sleep”, such as “pins and needles” and tingling. After the pressure cuff is released, a second scan will be taken of the artery.
3. **Retinal image:** After resting in a dark room for 5 minutes, you will be asked to place your chin on a rest in front of the camera. We will take photos of the back of both of your eyes. Glasses or contacts have to be removed for this test. Please bring your personal contact container and solutions.

Initial/Date _____

4. **Venous blood samples:** Approximately 60 ml of blood will be drawn (about 4 tablespoons) by a registered nurse or an experienced study personnel for data analysis. A small portion of the blood (approximately 5 ml) will be used for genotyping of GSTM1. Please see the genotyping consent (PCS-4). With your permission (consent form PCS-2), we may also store some of your blood that we obtained during the study for yet-to-be-determined tests in the future.
5. **TracMyAir:** The TracMyAir App will be used by study personnel each day you visit the EPA health study facility. The App will not be installed on your phone. The study staff will ask you questions on your home building characteristics, home operating conditions, time-spent in different outdoor and indoor environments, and time-spent at different physical activity levels to calculate your exposure to air pollution. The study personnel will input data for you into the App on an EPA provided smartphone. TracMyAir does not save the calculated exposures on the smartphone and the data is de-identified.
6. **Spirometry:** You will breathe through a filter into a clinical machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times. This test measures the volume of air that can be exhaled and the rate of airflow during exhalation after a maximal inhalation.

If there are any samples left over after all study information is collected, we will continue to store the samples for as yet undesignated studies. This allows us to make the best use of the samples we collect from subjects. **You will be given a separate consent form (Form PCS-2) for this storage, and you do not have to allow your samples to be stored indefinitely in order to participate in this study.**

What are the possible benefits from being in this study?

You will not benefit directly from being in this research study, though by participating in this study, you will receive a medical examination that includes blood work, lung function test, and ECG monitoring of your heart at no charge. However, this is not a substitute for a routine doctor visit. The medical staff will explain to you any remarkable findings regarding your overall health status. In addition, if we observe changes in your health status as a consequence of exposure to air pollutants, you may elect to use this information to avoid exposure on high pollution days.

This research is designed to benefit society by gaining new knowledge. Given that every member of American society is currently exposed to air pollution, this study has the potential to contribute to devising effective strategies aimed at protecting millions from the untoward effects of these pollutants.

What if we learn about new risks during the study?

You will be given any new information that becomes available during the course of the study that might affect your informed consent and your willingness to continue your participation.

What are the possible risks or discomforts involved with being in this study?

Initial/Date _____

This study might involve the following risks and/or discomforts to you:

- **Heart rate variability (HRV) measurements:** You may have minor skin irritation in the area where the electrodes are attached to the skin. Prior to electrode application, the skin will be treated with alcohol and a cleansing solution. If you are male, the skin may be shaved in the area where the electrodes are attached. You should not participate if your skin is highly sensitive to electrode adhesive or gel. Itching or burning occurs in some people. It is also possible for discoloration from the taped area to occur. If these symptoms persist or worsen, you should contact the medical station immediately.
- **Brachial artery ultrasound (BAU):** There are no significant risks associated with ultrasound imaging of the brachial artery, or with brief episodes of reduced or interrupted blood flow to your forearm. Stopping the blood flow to the arm may result in mild discomfort or temporary sensations of tingling or numbness in the hand until the blood pressure cuff is released (very common). About 1 in 200 patients develop a painless rash on the arm where the blood pressure cuff is placed; this disappears over several days. Some risks and discomforts may be unforeseeable.
- **Blood sampling:** Drawing blood from the vein in your arm will be performed by a registered nurse or an experienced study personnel and entails a risk of mild discomfort with the possibility of a small swelling or bruise. A very small risk of infection at the puncture site or in the blood vessel exists. You will have one blood draw each study session (usually on the 2nd visit day). The total amount of blood per blood draw is approximately 60 ml (about 4 tablespoons) each study session.
- **Spirometry (pulmonary function tests):** You may cough or become dizzy during these tests. You will be seated in a chair, and if these symptoms occur, they are usually only temporary.
- **Retinal image:** There is little risk associated with taking a photograph of your retina. The most likely discomfort is momentary visual impairment caused by the firing of the flash used by the camera.
- **Consumption of dietary fish oil supplements:** We do not want to interfere with your current dietary routine. If you are taking fish oil per prescription, please follow your doctor's orders. Dietary fish oil supplements are relatively safe as a whole. High-dose of fish oil may increase bleeding times and may cause stomach upset.
- **GPS recorder:** You may be concerned about the GPS travel recorder because it will be continuously recording your location. But the information on this device is secure and it is not available on any type of screen. Your location information is only stored internally on the device and there is no display or remote control for this unit. After your session, the information will be cleared from the device, and data will be transferred into a secure computer using a cable connection. The data can only be read by a very specific computer program.
- **Hexoskin:** There is little risk associated with wearing the compression shirt overnight. . The information on this recorder is secure and it is not available on any type of screen. Your information is only stored internally on the recorder and there is no display or remote control for this unit. After your session, the information will be cleared from the device, and data will be transferred into a secure computer using a cable connection.
- **TrackMyAir:** There is little risk associated with answering the question presented by the application. All data is de-identified and not stored on the study specific device.

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- **Confidentiality:** Risk of breach of confidentiality is minimal. All individuals who have been granted access to the data to perform their research-related duties will be bound by an agreement of confidentiality. You will be assigned a study number which will be used for data recording – not your name. The study number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has monitored access 24 hours/day. Any abnormal medical findings (CBC, ECG) will be discussed directly with you and you will be counseled to seek treatment from your personal physician at your own expenses if indicated. All samples will be stored at the U.S. EPA Human Studies Facility.

In addition, there may be uncommon or previously unrecognized risks that might occur. If you do notice any unusual symptoms occurring during the study you should call the EPA medical station 919-966-6232.

How will your privacy be protected?

You will be given a study code number. All electronic documents will only have that number. The paper records that the coordinators and medical doctors use may have your name. Your information can be linked to your personal information by the study number, however only study personnel have access to your personal information. Paper records that use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week. Blood samples will be stored at the EPA Human Studies Facility.

Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No subjects will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

What will happen if you are injured by this research?

All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. If such problems occur, we have physicians and nurses in the building at all times who will provide emergency care as needed. They may also refer you to a local health care facility.

If you develop an injury or illness determined by the on duty physician to be due to your participation in this research, the EPA will reimburse your medical expenses to treat the injury or illness up to \$5000. If you believe your injury or illness was due to a lack of reasonable care or

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other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et. seq., provides for money damages against the United States when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?

The total compensation for completion of the study will be \$1125. This amount reflects both the procedures or tests involved, and the time required to participate. If you are unable to complete the study for voluntary reasons or failure to comply with eligibility requirements you will be compensated for your participation up to that point. The amount of compensation for each study visit is broken down as shown below.

We anticipate performing several tests on you during the course of this study. However, circumstances beyond our control may arise (i.e. equipment failure) which may prevent us from performing a specific test on you. If we are unable to perform a specific test on you which is a primary endpoint for us, you will be compensated for all tests and time completed on that day and rescheduled. If this test is a secondary endpoint for us and is also a source of compensation, you will be paid for that test, but not rescheduled to make up the procedure.

In addition, you will be reimbursed for mileage at the current government rate if you live outside of the Chapel Hill/Carrboro area, and for parking costs while at the research facility. Money received by participants in research studies is normally treated as ordinary income by taxing authorities and we will report payments made to you to the Internal Revenue Service as required by law. Payments totaling more than \$600 in a year from a single or multiple EPA studies will be reported to the IRS. This summary is to emphasize the importance of all the visits, and to signify the importance of your time and commitment to the research study. The following table details the compensation for completion of the study on a day-by-day basis:

Study session 1

1st day visit (approximately 4 hours)	\$50
<ul style="list-style-type: none">• Vital signs check• Informed consent (Form PCS-1 to Form PCS-5)• Urine test• A Residence and Participant Survey (Form PCS-9)• TracMyAir• A baseline dietary food frequency questionnaire (online access) instruction (Form PCS-12) and dietary counseling on portion size (Form PCS-8)• A list of Low Fat Breakfast and Lunch Choices (Form FCS-11)• Spirometry training	

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- Heart rate variability (HRV)
- GPS recorder, activity monitor and Hexoskin placement

2nd day visit (approximately 3 hours) **\$150**

- Vital signs check
- Blood draw
- HRV
- BAU
- Retinal image
- Spirometry
- A Daily Follow-up Questionnaire (Form PCS-10)
- TracMyAir

Study session 2-5

1st day visit (approximately 2 hours) **\$50**

- Vital signs check
- Urine test
- Dietary 24 h recall (Form PCS-7)
- TracMyAir
- HRV
- GPS monitor, activity monitor and Hexoskin placement

2nd day visit (approximately 3 hours) **\$150**

- Vital signs check
- Blood draw
- HRV
- BAU
- Retinal image
- Spirometry
- A Daily Follow-up Questionnaire (Form PCS-10)
- TracMyAir

Study completion **\$125**

- Food frequency questionnaire
- Study completion bonus

Maximum payment = \$1125

You should understand that your participation is voluntary. You may terminate your participation in the study at any time without penalty. If you voluntarily elect to withdraw from the study at any time or you fail to maintain compliance with eligibility requirements, you will be paid for that portion of the study that has been completed.

Initial/Date _____

In the event a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, you will be paid \$12 per hour for the time scheduled and canceled. You will be paid in full for any procedures that may have been started during the current visit. Cancellations could occur due to adverse weather conditions, equipment failure, and other unforeseen events. When feasible, canceled visits will be rescheduled.

The investigators also have the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, or because the entire study has been stopped, or for some other reason.

Will it cost you anything to be in this study?

There will be no cost to you for participating in the study. However, if you are deemed not eligible to participate in the study for medical reasons, we may suggest that you seek follow-up care from your own health care provider for abnormalities discovered during the screening history, physical examination, or the study. **Such care is entirely at your own expense. EPA will not provide reimbursement for any follow-up care.**

All study procedures will be paid for by the study. We will give you parking coupons to cover the cost of parking. If you live beyond Chapel Hill/Carrboro you will be reimbursed for mileage at the US Government mileage rate in effect at the time.

What if you are a UNC student?

You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?

Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?

This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have further questions regarding this study, you should call one of the listed investigators on the first page of this form.

If you feel a research-related injury has occurred, please contact the Human Studies Facility medical station or one of the investigators listed above. In addition, you should contact the Human Studies Division Human Research Officer and Director of the National Health Effects and Environmental Research Laboratory Human Research Protocol Office at 919-966-6217.

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What if you have questions about your rights as a research subject?

All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

IRB Study # 16-1048

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily **AGREE** to participate in this research study.

Signature of Research Participant

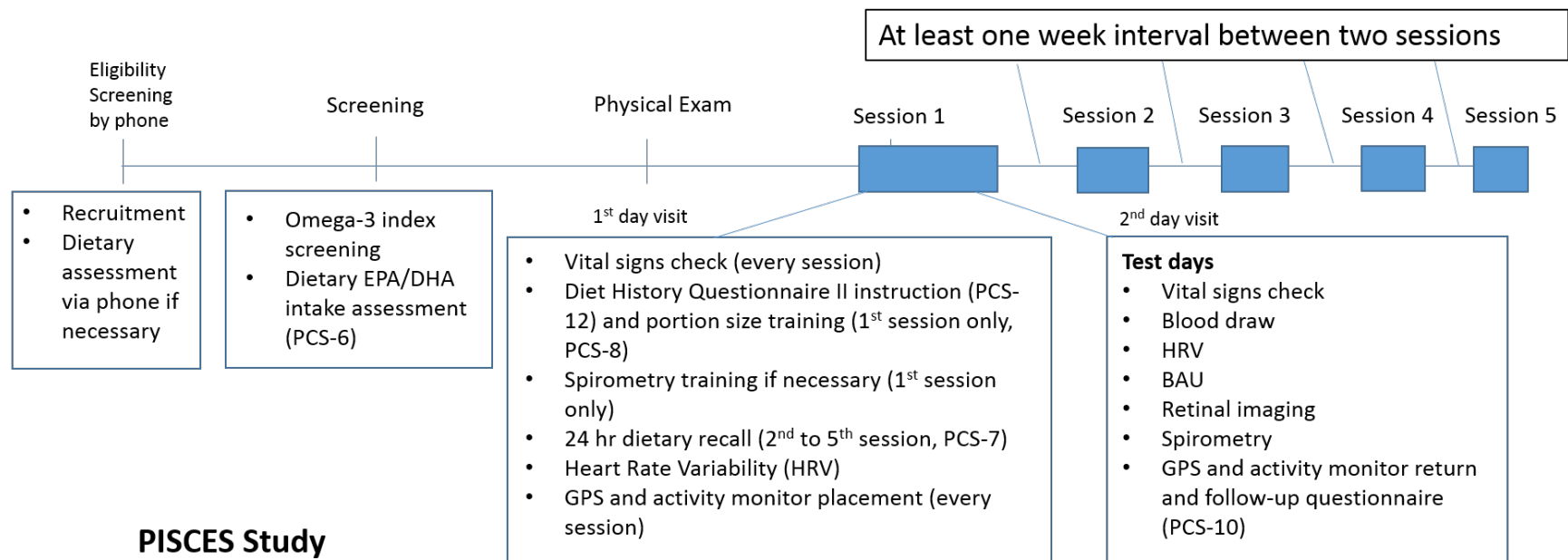
Date

Printed Name of Research Participant

Signature of Research Team Member Obtaining Consent

Date

Printed Name of Research Team Member Obtaining Consent



University of North Carolina at Chapel Hill
Consent Checklist

IRB Study # 16-1048

Consent Form Version Date: 11.15.2018

PCS
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Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Co-Principal Investigators: James Samet, PhD, MPH; Hao Chen, PhD

UNC-Chapel Hill Department: US Environmental Protection Agency

Principal Investigator Email Address: tong.haiyan@epa.gov

Funding Source: US Environmental Protection Agency Intramural Federal Research

Study Contact telephone number: (919) 966-4993, (919) 966-0665, (919) 966-9427

Study Contact email: tong.haiyan@epa.gov; samet.james@epa.gov; chen.hao@epa.gov.

_____ I have read the consent form titled, “*Consent to Participate in a Research Study*” for the study titled, “*Effects of omega-3 fatty acids in Ambient Air Pollution Exposure in Healthy Adult*”.

_____ A member of the study team has reviewed the consent form titled, “*Consent to Participate in a Research Study*” for the study titled, “*Effects of omega-3 fatty acids in Ambient Air Pollution Exposure in Healthy Adult*” with me.

_____ I was given the opportunity to ask a member of the study team questions about the study and my involvement in the study.

_____ I have been made aware that the purpose of this research study is to determine if dietary consumption of omega-3 fatty acids (such as dietary fish oil supplements) affects heart and lung responses to ambient air pollution in healthy adults.

_____ I understand that there are risks associated with my participation in this study. A study team member has discussed potential risks associated with participation in this study, and the measures that will be taken by the study team to reduce risk, with me.

_____ A member of the study team has discussed genotyping with me and I have been given the opportunity to either opt-in or opt-out of being genotyped as a part of this study.

_____ I understand that I have the ability to terminate my involvement in the study at any time for any reason and that I am under no obligation to complete the study.

_____ A member of the study team has reviewed the form, “*Consent for Storing Biological Specimens with Identifying Information*” with me and explained how, with my consent, blood samples taken from me during the course of this study will be stored.

Initial/Date _____

_____ I understand that I can submit a written request at any time, during or after the completion of this study, to the Principle Investigator asking for my specimens to be destroyed.

_____ I have been made aware that if I choose to end my involvement in the study prior to completion of my study-related visits/activities, I will receive compensation at 100% of the indicated rate through the last day that I participated in the study.

_____ I have been given contact information for the Principal Investigator and the Medical Station at the EPA Human Studies Facility.

_____ I understand that I can ask a member of the study team or the medical staff a question regarding the study and my involvement in the study at any time.

_____ I have had an opportunity to ask a member of the study team any questions that I have up to this point regarding the study and my involvement in the study.

IRB Study # 16-1048

Title of study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adult.

Principal investigator: Haiyan Tong, MD, PhD.

Subject's Agreement:

I verify that, to the best of my knowledge and belief, all of the information contained in the consent form was read and understood by me prior to signing it. I further certify that I have read the information above and by initialing at each statement and signing below I acknowledge that I agree and understand each statement above. I have asked all the questions I have at this time.

Signature of Research Subject

Date

Printed Name of Research Subject

Signature of Research Team Member Obtaining Consent

Date

Printed Name of Research Team Member Obtaining Consent

University of North Carolina at Chapel Hill
Consent for Genotyping With Identifying Information

IRB Study # 16-1048

Consent Form Version Date: 11.15.2018

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Co-Principal Investigators: James Samet, PhD, MPH; Hao Chen, PhD

UNC-Chapel Hill Department: US Environmental Protection Agency

Principal Investigator Email Address: tong.haiyan@epa.gov

Funding Source: US Environmental Protection Agency Intramural Federal Research

Study Contact telephone number: (919) 966-4993, (919) 966-0665, (919) 966-9427

Study Contact email: tong.haiyan@epa.gov; samet.james@epa.gov; chen.hao@epa.gov.

What are some general things you should know about this research study?

Research studies are designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help to develop new products, such as drugs.

You may refuse to allow us to have or store your specimen. If you are a patient with an illness, you do not have to be in the research study in order to receive treatment.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The glutathione S-transferase mu 1 (GSTM1) is of interest in this study, because recent reports have shown that people with the GSTM1 null gene, are more susceptible to air pollutants. The GSTM1 gene plays an important role in the response to oxidative stress and inflammation in the lung. Present evidence suggests that GSTM1 null genotype is highly prevalent in the population, and associated with increased risk of asthma incidents among children, and the development of chronic obstructive pulmonary disease (COPD) in adults, when these populations are exposed to environmental tobacco smoke or secondhand smoke, ambient air pollutants such as ozone and diesel exhaust particles, or endotoxin and other pathogen-associated particles. The main purpose

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of this research study is to determine whether dietary omega-3 fatty acids can modify the cardiovascular (heart and blood vessels) and pulmonary (lungs) effects to ambient air pollution in healthy adults. The purpose of the genotyping is to determine whether a subject carries the GSTM1 sufficient or GSTM1 null genotypes. We will analyze the data at the end of the study, and determine whether GSTM1 genotype influenced the cardiovascular and pulmonary effects to ambient air pollution in healthy adults who consume high or low levels of fish oil. Your participation to this genotyping test will not affect your eligibility to participate in this research study.

How many subjects will participate in this study?

If you decide to participate, you will be one of approximately 60 participants in this study.

What will happen if you participate in this study?

We will briefly review your medical history and any medical conditions that you have or medications that you are currently taking. You will sign 2 copies of the study consent form. We will measure your blood pressure and draw approximately 60 ml (about 4 tablespoons) of blood for blood analysis and genotyping. A small portion of your blood (about 5 ml) will be used for genotyping.

If you have been genotyped before, there will be no genotyping this time.

How will the blood sample be collected?

You will have approximately 60 ml (about 4 tablespoons) of blood taken by a registered nurse or an experienced personnel.

What will happen to the blood?

A portion of the blood sample (about 5 ml) collected will be used to look at the GSTM1 gene and another portion of the blood will be used for cholesterol, lipid and other blood analysis. With your permission, if there are excess samples left over after use for the purposes of this specific study, they will be stored at the U.S. Environmental Protection Agency Human Studies Facility located in Chapel Hill North Carolina. Only project members of the study will have access to the samples.

During the course of this research, other researchers may request access to specimens for as-of-yet unspecified research that may or may not be related to the original research from which the specimens were derived. In these cases, provided appropriate IRB approved consent has been obtained from subjects, these specimens will be provided without identifiers to these other researchers by employing a data use agreement.

Are there any reasons you should not participate?

You should not participate in this portion of the study if you are not a candidate for the subsequent portions. The inclusion and exclusion criteria has been described in the main study consent form. Briefly, you should not have chronic diseases including cardiovascular diseases, active allergies, lung diseases, diabetes, and uncontrolled high blood pressure. You should not be currently taking β -blockers (such as atenolol, metoprolol, propranolol, acebutolol) and statins. You should not be currently smoking or have a smoking history within 1 year of the study (defined as more than one pack of cigarettes in the past year) or have a greater than/equal to a 5

Initial/Date _____

pack year smoking history. The investigators and medical staff will explain other potential exclusionary conditions in detail to you.

What are the possible benefits to you?

There are no direct benefits to you for completing this portion of the study. However, you will know your blood cholesterol levels and you will know your genotype of GSTM1 gene.

What are the possible risks or discomforts involved with being in this study?

This study might involve the following minimal risks and/or discomforts to you:

1. The risks associated with taking blood samples are considered minimal. A registered nurse will draw the blood. Drawing blood could cause some bruising or minor pain, which usually resolves quickly. Also, a rare complication is skin infection or an infection of the vein in which the blood has been drawn. The risk of getting an infection is minimized by the use of sterile technique. If you do have signs of infection at the site (redness, warmth, painful skin, and swelling) after completion of the procedure, you will need to contact the EPA medical station.
2. Risk of breach of confidentiality is minimal. You will be assigned a study number which will be used for data – not your name. The study number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers

Will there be any cost to you to participate?

The U.S. EPA will pay the costs of this research. You will not be billed for any procedures.

Will you receive anything for being in this study?

You will be paid for participation in the study. We will give you parking coupons to cover the cost of parking. If you live outside of the Chapel Hill/Carrboro area, you will be reimbursed for mileage at the current government rate.

Who owns the blood samples?

Any blood samples obtained for the purpose of this study become the exclusive property of The U.S. Environmental Protection Agency. The researchers may retain, preserve or dispose of these specimens and may use these specimens for research that may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens.

How will your privacy be protected?

You will be given a study code number. All electronic documents will only have that number. The paper records that the coordinators and medical doctors use may have your name. Your information can be linked to your personal information by the study number, however only study personnel have access to your personal information. Paper records which use your name are kept

Initial/Date _____

in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week. Samples used for genetic analysis will be stored at the EPA Human Studies Facility.

Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No one will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

Will researchers seek approval from you to do future studies involving the blood samples?

By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants.

In some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

Will you receive study results of future research involving your blood samples?

Most research with your specimens is not expected to yield new information that would be meaningful to share with you individually. In rare cases, you may be offered the opportunity to receive information about the results of research in which the specimens were used (for example, findings that would affect your medical care).

Can you withdraw the blood samples from the research study?

If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. You may also contact the Institutional Review Board, University of North Carolina at Chapel Hill, 919-966-3113, Medical School Building 52, CB 7097, Chapel Hill, NC 27599, or by email at IRB_subjects@unc.edu. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

Initial/Date _____

What will happen if you are injured by this research?

All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. If you develop an injury or illness determined by the on duty physician to be due to your participation in this research, the EPA will reimburse your medical expenses to treat the injury or illness up to \$5000. If you believe your injury or illness was due to a lack of reasonable care or other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et. seq., provides for money damages against the United States when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

If a research related injury or illness occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919.966.6217.

Who is sponsoring this study?

This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, you should contact the researchers listed on the first page of this form or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

What if you have questions about your rights as a research subject?

All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

Genetic Information Nondiscrimination Act Guidance

Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Initial/Date _____

IRB Study # 16-1048

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Subject's Agreement:

I have read the information provided above in the Genotyping With Identifying Information form for the IRB study # 16-1048. I have asked all the questions I have at this time.

☐ I **AGREE** to my specimen(s) being used for genotyping with the identifying code(s).

☐ I **DO NOT AGREE** to my specimen(s) being used for genotyping with the identifying code(s).

Signature of Research Participant

Date

Printed Name of Research Participant

Signature of Research Team Member Obtaining Consent

Date

Printed Name of Research Team Member Obtaining Consent

University of North Carolina at Chapel Hill
Consent for Omega-3 Index Screening With Identifying Information

IRB Study # 16-1048

Consent Form Version Date: 4.12.2018

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Co-Principal Investigators: James Samet, PhD, MPH; Wan Shen, PhD, RDN, LDN.

UNC-Chapel Hill Department: US Environmental Protection Agency

Principal Investigator Email Address: tong.haiyan@epa.gov

Funding Source: US Environmental Protection Agency Intramural Federal Research

Study Contact telephone number: (919) 966-4993, (919) 966-0665, (919) 843-9228

Study Contact email: tong.haiyan@epa.gov; samet.james@epa.gov; shen.wan@epa.gov.

What are some general things you should know about this research study?

Research studies are designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help to develop new products, such as drugs.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The main purpose of this research study is to determine if dietary consumption of Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA), two important omega-3 fatty acids, affects cardiopulmonary responses to ambient air pollution in healthy adults. Results from this study will expand our knowledges in utilizing dietary strategies to combat the adverse effects of exposure to air pollution.

The primary purpose of today's visit is to determine the level of EPA and DHA fatty acids in your blood, the results of which will determine your eligibility to participate in this study.

In addition, we will further assess your dietary patterns as they pertain to your intake of omega-3 fatty acids by asking you to complete a questionnaire.

Initial/Date _____

What will happen if you participate this portion of the study?

First, you will read this consent form (Form PCS-14) and have this portion of the study described to you. You will be given the opportunity to have any questions answered before signing the consent forms. After signing the consent form, you will complete a questionnaire designed to assess your EPA and DHA dietary intake (Form PCS-6). You will have your weight and height measured at medical station. You will then be asked to wash your hands thoroughly and a small sample of your blood (between approximately an eighth to a quarter of a teaspoon) will be collected by pricking one of your fingers using a finger stick device. The blood sample will be collected by the experienced study investigator.

What will happen to the blood?

The sample will be used to measure the relative content of various fatty acids, including EPA and DHA, present in your blood.

What are the possible benefits to you?

There are no direct benefits to you for completing this portion of the study. However, you will learn about the fatty acids in your blood and have an opportunity to have any questions answered by the study personnel.

What are the possible risks or discomforts involved with being in this study?

This study might involve the following minimal risks and/or discomforts to you:

1. The risks associated with taking the blood sample is considered minimal. A registered nurse or other experienced study investigator will prick your finger using a special finger stick device designed for this purpose in order to collect the blood. The finger prick and blood collection procedure often causes momentary discomfort. Some minor bruising, which usually resolves quickly, is also possible. There is a small risk of infection. This risk is minimized by the use of sterile technique. If you develop signs of infection at the site of blood collection (redness, warmth, painful skin, or swelling), you should contact the EPA medical station immediately. In some cases, a person may faint or become sick to the stomach at the sight of blood is being collected.
2. Risk of breach of confidentiality is minimal. You will be assigned a screening number which will be used for this process – not your name. The number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers.

Will there be any cost to you to participate?

There will be no cost to you for participating in the study. However, if you are deemed not eligible to participate in the study for medical reasons, we may suggest that you seek follow-up care from your own health care provider for abnormalities discovered during the screening

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history, physical examination, or the study. **Such care is entirely at your own expense. EPA will not provide reimbursement for any follow-up care.**

Will you receive anything for being in this study?

You will be paid \$20 for participation in this portion of the study. We will give you parking coupons to cover the cost of parking. If you live outside of the Chapel Hill/Carrboro area, you will be reimbursed for mileage at the current government rate.

How will your privacy be protected?

You will be given a screening number. All electronic documents will only have that number. The paper records that the coordinators and medical staff use may have your name. Your information can be linked to your personal information by the screening number, however only study personnel have access to your personal information. Paper records which use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week.

No one will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

What will happen if you are injured by this research?

All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. If you develop an injury or illness determined by the on duty physician to be due to your participation in this research, the EPA will reimburse your medical expenses to treat the injury or illness up to \$5000. If you believe your injury or illness was due to a lack of reasonable care or other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et. seq., provides for money damages against the United States when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

If a research related injury or illness occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919.966.6217.

What if you are a UNC student?

You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

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What if you are a UNC employee?

Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?

This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, you should contact the researchers listed on the first page of this form or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

What if you have questions about your rights as a research subject?

All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

Initial/Date _____

IRB Study # 16-1048

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate.

Signature of Research Participant

Date

Printed Name of Research Participant

Signature of Research Team Member Obtaining Consent

Date

Printed Name of Research Team Member Obtaining Consent

PCS 3

**University of North Carolina at Chapel Hill
Consent to Re-Contact Following Removal From the Study
Re-contact Consent**

IRB Study # 16-1048

Consent Form Version Date: 11.15.2018

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Co-Principal Investigators: James Samet, PhD, MPH; Hao Chen, PhD

UNC-Chapel Hill Department: US Environmental Protection Agency

Principal Investigator Email Address: tong.haiyan@epa.gov

Funding Source: US Environmental Protection Agency Intramural Federal Research

Study Contact telephone number: (919) 966-4993, (919) 966-0665, (919) 966-9427

Study Contact email: tong.haiyan@epa.gov; samet.james@epa.gov; chen.hao@epa.gov

You have previously given consent to participate in this study. As an added measure to protect your safety, we would like to have your permission to contact you to follow-up on your health if you are removed from the study for safety/medical reasons. If you are removed from the study for safety/medical reasons, then a member of the study team will contact you within 30 days of your removal from the study to follow-up on the concern that led to your removal from the study.

The purpose of this form is to gain your permission to contact you after your removal from the study if you are removed for safety/medical reasons. By signing this form you acknowledge that you have read this form in its entirety and a member of the study team has explained the change in the study protocol. You also acknowledge that all of the terms of any consent forms that you have previously signed regarding this study still apply.

IRB Study # 16-1048

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Participant's Agreement:

I have read the information provided above in the Re-contact form for the IRB study # 16-1048. I have asked all the questions I have at this time.

☐ I **AGREE** to be contacted by a study team member within 30 days of my removal from the study if I am removed for safety/medical reasons.

☐ I **DO NOT AGREE** to be contacted by a study team member within 30 days of my removal from the study if I am removed for safety/medical reasons.

Signature of Research Participant

Date

Printed Name of Research Participant

Signature of Research Team Member Obtaining Consent

Date

Printed Name of Research Team Member Obtaining Consent

IRB Study # 16-1048

Consent Form Version Date: 11.15.2018

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

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UNC-Chapel Hill Department: US Environmental Protection Agency

Principal Investigator Email Address: tong.haiyan@epa.gov

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Study Contact email: tong.haiyan@epa.gov; samet.james@epa.gov; chen.hao@epa.gov.

What are some general things you should know about this research study?

Research studies are designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help develop new products, such as drugs.

You may refuse to allow us to have or store your specimen. If you are a patient with an illness, you do not have to be in the research study in order to receive treatment.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

Air pollution exposure has been found to cause a range of lung and systemic changes in normal subjects. We will be collecting blood samples which will help us to further study this condition. In order to do so, we will need to collect and store blood. Blood samples will be collected in order to look for but not limited to indicators of inflammation due to the air pollution exposure.

All samples will be stored where only project members will have access to the samples. There is a need to store samples in such a repository because this will be an ongoing study where samples from subjects will be collected over an extended period of time. Storing of samples allows for

Initial/Date _____

all samples to be processed at the same time and also allows our scientist the opportunity to further study these samples with as yet unknown questions and techniques.

How will the specimen be collected?

The description of the samples to be collected and the manner in which this will be done have been described in the main study consent.

What will happen to the specimen?

Blood samples will be collected in order to look at but not limited to, indicators of inflammation due to the air pollution exposure. If there are excess samples left over after use for the purposes of this specific study, they will be stored at the U.S. Environmental Protection Agency Human Studies Facility located in Chapel Hill North Carolina. Only project members of the study will have access to the samples.

During the course of this research, other researchers may request access to specimens (or data) for as-of-yet unspecified research that may or may not be related to the original research from which the specimens were derived. In these cases, provided appropriate IRB approved consent has been obtained from subjects, these specimens (or data) will be provided without identifiers to these other researchers by employing a data use agreement.

What are the possible benefits to you?

You will not benefit directly from being in this research study. This is not a substitute for a routine doctor visit.

This research is designed to benefit society by gaining new knowledge. Given that every member of American society is currently exposed to these pollutants, this study has the potential to contribute to devising effective strategies aimed at protecting millions from the untoward effects of these pollutants.

What are the possible risks or discomforts involved with being in this study?

This study might involve the following risks and/or discomforts to you:

1. Blood sampling will be performed by an experienced study personnel, and entails only a risk of mild discomfort with the infrequent possibility of lightheadedness, fainting, infection or developing a bruise.
2. Risk of breach of confidentiality is minimal. You will be assigned a study number which will be used for data – not your name. The study number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers

Initial/Date _____

Will there be any cost to you for storage of the specimens?

There will be no cost to you for the storage and use of the specimens for research purposes.

Will you receive anything for being in this study?

You will not receive anything for taking part in this study with regard to storage of excess specimens. Reimbursement for participation in the main study is addressed in the detailed consent for that study.

Who owns the specimens?

Any blood, body fluids, or tissue specimens obtained for the purpose of this study become the exclusive property of The U.S. Environmental Protection Agency. The researchers may retain, preserve or dispose of these specimens and may use these specimens for research that may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens.

How will your privacy be protected?

You will be given a study code number. All electronic documents will only have that number. The paper records that the coordinators and medical doctors use may have your name. Your information can be linked to your personal information by the study number, however only study personnel have access to your personal information. Paper records which use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week. Samples used for genetic analysis will be stored at the EPA Human Studies Facility.

Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No one will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

Will researchers seek approval from you to do future studies involving the specimens?

By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants.

In some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

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Will you receive study results of future research involving your specimens?

Most research with your specimens is not expected to yield new information that would be meaningful to share with you individually. In rare cases, you may be offered the opportunity to receive information about the results of research in which the specimens were used (for example, findings that would affect your medical care).

Can you withdraw the specimens from the research study?

If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. You may also contact the Institutional Review Board, University of North Carolina at Chapel Hill, 919-966-3113, Medical School Building 52, CB 7097, Chapel Hill, NC 27599, or by email at IRB_subjects@unc.edu. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

What will happen if you are injured by this research?

All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. If you develop an injury or illness determined by the on duty physician to be due to your participation in this research, the EPA will reimburse your medical expenses to treat the injury or illness up to \$5000. If you believe your injury or illness was due to a lack of reasonable care or other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et. seq., provides for money damages against the United States when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

If a research related injury or illness occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217.

Who is sponsoring this study?

This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, you should contact the researchers listed on the first page of this form or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

Initial/Date _____

What if you have questions about your rights as a research subject?

All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

IRB Study # 16-1048

Title of Study: Effects of Omega-3 Fatty Acids in Ambient Air Pollution Exposure in Healthy Adults

Principal Investigator: Haiyan Tong, MD, PhD

Subject's Agreement:

I have read the information provided above in the Storing Biological Specimens with Identifying Information form for the IRB study # 16-1048. I have asked all the questions I have at this time.

☐ I **AGREE** to my specimen(s) being stored with the identifying code(s).

☐ I **DO NOT AGREE** to my specimen(s) being stored with the identifying code(s).

Signature of Research Participant

Date

Printed Name of Research Participant

Signature of Research Team Member Obtaining Consent

Date

Printed Name of Research Team Member Obtaining Consent